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(54) Title: HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract: In accordance with the present invention, there are provided novel class of heterocyclic compounds and methods of use thereof. Compounds of the invention contain a substituted, unsaturated five, six or seven membered heterocyclic ring that includes at least one nitrogen atom and at least one carbon atom. At a ring position adjacent to a ring nitrogen atom, the heterocyclic ring has at least one substituent which includes a moiety, linked to the heterocyclic ring via an alkylene moiety, an alkynylene moiety or an azo group. Invention compounds are capable of a wide variety of uses including modulating physiological processes by functioning as agonists and antagonists of receptors in the nervous system, as insecticides, and as fungicides. The invention further provides methods of modulating the activity of excitatory amino acid receptors using a specifically defined class of heterocyclic compounds including the novel compounds referred to above. In one embodiment, there are provided methods of modulating metabotropic glutamate receptors. The present invention also discloses methods of treating disease using heterocyclic compounds. The invention further discloses methods of preventing disease conditions related to diseases of the pulmonary system, diseases of the nervous system, diseases of the cardiovascular system, diseases of the gastrointestinal system, diseases of the endocrine system, diseases of the exocrine system, diseases of the skin, cancer and diseases of the ophthalmic system. The invention also discloses pharmaceutically acceptable salt forms of the above-described heterocyclic compounds.

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HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

FIELD OF INVENTION

The present invention relates to novel heterocyclic compounds which contain a heterocylic ring bearing at least one substituent attached by a linker containing an acetylenic group, a vinylic group or an azo group. In addition, the present invention relates to therapeutic methods of use of heterocyclic compounds for the treatment and prevention of various disease conditions.

BACKGROUND OF THE INVENTION

Unsaturated heterocylic compounds find a wide variety of uses. For example, compounds of this class find uses as modulators of physiological processes that are mediated by ligand-activated receptors. Receptors that are activated by ligands are located throughout the nervous, cardiac, renal, digestive and bronchial systems, among others. Therefore, in the nervous system, for example, heterocyclic compounds are capable of functioning as agonists or antagonists of receptors for neurotransmitters, neurohormones and neuromodulators. Ligand-activated receptors have been identified in a wide variety of species, including humans, other mammals and vertebrates as well as in invertebrate species. Therefore, compounds of this class are also able to modulate receptor-mediated processes throughout phylogeny and find uses in a wide variety of applications, *e.g.*, as pharmaceuticals, insecticides and fungicides.

Receptors activated by excitatory amino acids, such as the amino acid L-glutamic acid (glutamate), are a major excitatory neurotransmitter receptor class in the mammalian central nervous system. Anatomical, biochemical and electrophysiological analyses suggest that glutamatergic systems are involved in a broad array of neuronal processes, including fast excitatory synaptic transmission, regulation of neurotransmitter release, long-term potentiation, long-term depression, learning and memory, developmental synaptic plasticity, hypoxic-ischemic damage and neuronal cell death, epileptiform seizures, visual processing, as well as the pathogenesis of several neurodegenerative disorders. See generally, Nakanishi *et al., Brain Research Reviews* 26:230-235 (1998); Monaghan *et al., Ann. Rev. Pharmacol. Toxicol.* 29:365-402 (1980). This extensive repertoire of functions, especially those related to learning, neurotoxicity, and neuropathology, has stimulated recent attempts to describe and define the mechanisms through which glutamate exerts its effects.

Glutamate has been observed to mediate its effects through receptors that have been categorized into two main groups: ionotropic and metabotropic. Metabotropic glutamate receptors are divided into three groups based on amino acid sequence homology, transduction mechanism and pharmacological properties, namely Group I, Group II and Group III. Each Group of receptors contains one or more types of receptors. For example, Group I includes metabotropic glutamate receptors 1 and 5 (mGluR1

and mGluR5), Group II includes metabotropic glutamate receptors 2 and 3 (mGluR2 and mGluR3) and Group III includes metabotropic glutamate receptors 4, 6, 7 and 8 (mGluR4, mGluR6, mGluR7 and mGluR8). Several subtypes of a mGluR type may exist. For example, subtypes of mGluR1 include mGluR1a, mGluR1b, mGluR1c and mGluR1d.

Anatomical studies demonstrate a broad and selective distribution of metabotropic glutamate receptors in the mammalian nervous system. For example, mGluR1 is expressed in the cerebellum, olfactory bulb, hippocampus, lateral septum, thalamus, globus pallidus, entopeduncular nucleus, ventral pallidum and substantia nigra (Petralia *et al.*, (1997) *J. Chem. Neuroanat.*, 13:77-93; Shigemoto *et al.*, (1992) *J. Comp. Neurol.*, 322:121-135). In contrast, mGluR5 is weakly expressed in the cerebellum, while higher levels of expression are found in the striatum and cortex (Romano *et al.*, (1995) *J. Comp. Neurol.*, 355:455-469). In the hippocampus, mGluR5 appears widely distributed and is diffusely expressed.

Metabotropic glutamate receptors are typically characterized by seven putative transmembrane domains, preceded by a large putative extracellular amino-terminal domain and followed by a large putative intracelluar carboxy-terminal domain. The receptors couple to G-proteins and activate certain second messengers depending on the receptor group. Thus, for example, Group I mGluRs activate phospholipase C. Activation of the receptors results in the hydrolysis of membrane phosphatidylinositol (4,5)-bisphosphate to diacylglycerol, which activates protein kinase C, and inositol trisphosphate, which in turn activates the inositol trisphosphate receptor to promote the release of intracellular calcium.

Ionotropic glutamate receptors are generally divided into two classes: the *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors. Both classes of receptors are linked to integral cation channels and share some amino acid sequence homology. GluR1-4 are termed AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors because AMPA preferentially activates receptors composed of these subunits, while GluR5-7 and KA1-2 are termed kainate receptors as these are preferentially sensitive to kainic acid. Thus, an "AMPA receptor" is a non-NMDA receptor that can be activated by AMPA. AMPA receptors include the GluR1-4 family, which form homo-oligomeric and hetero-oligomeric complexes which display different current-voltage relations and calcium permeability. Polypeptides encoded by GluR1-4 nucleic acid sequences can form functional ligand-gated ion channels. An AMPA receptor includes a receptor having a GluR1, GluR2, GluR3 and/or GluR4 subunit. A NMDA receptor includes a receptor having NMDAR1, NMDAR2a, NMDAR2b, NMDAR2c, NMDAR2d and/or NMDAR3 subunits.

Because of the physiological and pathological significance of excitatory amino acid receptors generally and metabotropic glutamate receptors, in particular, there is a need to identify methods of

modulating excitatory amino acid receptor-mediated processes, as well as therapeutic methods of treatment and methods for prevention of diseases. Also, there is a continuing need in the art for new members of a compound class that can modulate excitatory amino acid receptors. The present invention satisfies these and related needs.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel class of heterocyclic compounds. Compounds of the invention contain a substituted, unsaturated five-, six- or seven-membered heterocyclic ring that includes at least one nitrogen atom and at least one carbon atom. The ring additionally includes three, four or five atoms independently selected from carbon, nitrogen, sulfur and oxygen atoms. The heterocyclic ring has at least one substituent located at a ring position adjacent to a ring nitrogen atom. This mandatory substituent of the ring includes a moiety (B), linked to the heterocyclic ring via a hydrocarbyl or an azo group. The invention also discloses pharmaceutically acceptable salt forms of heterocyclic compounds.

Invention compounds are useful for a wide variety of applications. For example heterocyclic compounds can act to modulate physiological processes by functioning as agonists and antagonists of receptors in the nervous system. Invention compounds may also act as insecticides and as fungicides. Pharmaceutical compositions containing invention compounds also have wide utility.

In accordance with the present invention, there are also provided methods of modulating the activity of excitatory amino acid receptors using a specifically defined class of heterocyclic compounds. In one embodiment, there are provided methods of modulating metabotropic glutamate receptors. The present invention also provides methods of treating disease using heterocyclic compounds. Diseases contemplated include cerebral ischemia, chronic neurodegeneration, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of respiration, motor control and function, attention deficit disorders, concentration disorders, pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, eating disorders, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia and astrocytomas. The invention further discloses methods of preventing disease conditions related to diseases of the pulmonary system, diseases of the nervous system, diseases of the cardiovascular system, diseases of the gastrointestinal system, diseases of the endocrine system, diseases of the exocrine system, diseases of the skin, cancer and diseases of the ophthalmic system.

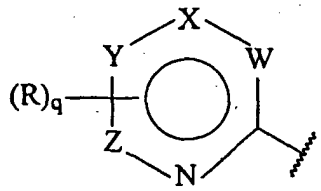
DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds having the structure:

A — L — B

or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein:

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of W, X, Y and Z is (CR)p, wherein p is 0, 1 or 2;

the remainder of W, X, Y and Z are each independently O, N or S; and

each R is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded:

the compounds wherein **A** is a 6-membered ring wherein:

W, X, Y and **Z** are $(CR)_p$ wherein p is 1; and

R at the W position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at the X position is hydrogen; R at the Y position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Z position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo,

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents; and

the compounds wherein A is a 6-membered ring wherein:

W, X, Y and Z are $(CR)_p$ wherein p is 1; R at the X position is not hydrogen; and R at the W, Y and Z positions are hydrogen;

L is alkenylene or alkynylene; and

B is a substituted or unsubstituted aryl or heterocycle containing two or more double bonds; and

the compounds wherein A is a 5-membered ring wherein:

one of W, X, Y and Z is $(CR)_p$, and p is 0, two of W, X, Y and Z are $(CR)_p$ and p is 1, and the remaining variable ring member is O or S; or

one of W, X, Y and Z is N, one of W, X, Y and Z is $(CR)_p$ and p is 1, one of W, X, Y and Z is $(CR)_p$ and p is 0, and the remaining variable ring member is O, S or $(CR)_p$, and p is 1; or

two of W, X, Y and Z are N, one of W, X, Y and Z is $(CR)_p$, and p is 0, and the remaining variable ring member is , O or S or $(CR)_p$, and p is 1;

each R is independently hydrogen, nitro, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, C_1-C_4-haloalkylthio, C_3-C_6-alkenyl or C_3-C_8-cycloalkyl;

L is alkynylene; and

B is substituted or unsubstituted aryl, wherein substituents are independently nitro, cyano, C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkthio, C_1-C_4-haloalkylthio, C_1-C_4-alkoxycarbonyl, C_3-C_6-alkenyl, phenyl or phenoxy, wherein phenyl and phenoxy may bear further substituents; and

the compounds wherein A is a 6-membered ring wherein:

W, X, Y and Z are (CR)p, wherein p is 1 and R is hydrogen,

L is alkynylene; and

B is unsubstituted 1-cyclopenten-1-yl or unsubstituted 1-cyclohexen-1-yl; and

the compounds wherein A is a 5-membered ring wherein:

W is (CR)p, and p is 0, **Y and Z** are (CR)p, and p is 1, **X** is N or S; and R is phenyl; or

W is (CR)p, and p is 0, **X and Z** are (CR)p, and p is 1, **Y** is O, N or S; and R is phenyl;

L is unsubstituted alkenylene and

B is unsubstituted phenyl; and

the compounds wherein **A** is a 5-membered ring containing two double bonds, wherein one of **W, X, Y** and **Z** is $(CR)_p$, and p is 0, and the remaining ring members are $(CR)_p$ and p is 1; and

the compounds wherein **A** is unsubstituted heterocycle containing two or more double bonds; **L** is alkenylene or alkynylene, and **B** is unsubstituted phenyl.

As employed herein, "hydrocarbyl" refers to straight or branched chain univalent and bivalent radicals derived from saturated or unsaturated moieties containing only carbon and hydrogen atoms, and having in the range of about 1 up to 12 carbon atoms. Exemplary hydrocarbyl moieties include alkyl moieties, alkenyl moieties, dialkenyl moieties, trialkenyl moieties, alkynyl moieties, alkadiynal moieties, alkatriynal moieties, alkenyne moieties, alkadienyne moieties, alkenediyne moieties, and the like. The term "substituted hydrocarbyl" refers to hydrocarbyl moieties further bearing substituents as set forth below.

As employed herein, "alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 12 carbon atoms; "substituted alkyl" refers to alkyl radicals further bearing one or more substituents such as hydroxy, alkoxy, mercapto, aryl, heterocycle, halogen, trifluoromethyl, pentafluoroethyl, cyano, cyanomethyl, nitro, amino, amide, amidine, amido, carboxyl, carboxamide, carbamate, ester, sulfonyl, sulfonamide, and the like.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 6 carbon atoms presently preferred), and "substituted alkenyl" refers to alkenyl radicals further bearing one or more substituents as set forth above.

As employed herein, "alkenylene" refers to straight or branched chain divalent alkenyl moieties having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms (with divalent alkenyl moieties having in the range of about 2 up to 6 carbon atoms presently preferred), and "substituted lower alkenylene" refers to divalent alkenyl radicals further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 6 carbon atoms presently being preferred), and "substituted alkynyl" refers to alkynyl radicals further bearing one or more substituents as set forth above.

As employed herein, "alkynylene" refers to straight or branched chain divalent alkynyl moieties having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with divalent alkynyl moieties having two carbon atoms presently being preferred), and "substituted alkynylene" refers to divalent alkynyl radicals further bearing one or more substituents as set forth above.

As employed herein, "cyclohydrocarbyl" refers to cyclic (*i.e.*, ring-containing) univalent radicals derived from saturated or unsaturated moieties containing only carbon and hydrogen atoms, and having in the range of about 3 up to 20 carbon atoms. Exemplary cyclohydrocarbyl moieties include cycloalkyl moieties, cycloalkenyl moieties, cycloalkadienyl moieties, cycloalkatrienyl moieties, cycloalkynyl moieties, cycloalkadiynyl moieties, spiro hydrocarbon moieties wherein two rings are joined by a single atom which is the only common member of the two rings (*e.g.*, spiro[3.4]octanyl, and the like), bicyclic hydrocarbon moieties wherein two rings are joined and have two atoms in common (*e.g.*, bicyclo [3.2.1]octane, bicyclo [2.2.1]hept-2-ene, norbornene, decalin, and the like), and the like. The term "substituted cyclohydrocarbyl" refers to cyclohydrocarbyl moieties further bearing one or more substituents as set forth above.

As employed herein, "cycloalkyl" refers to ring-containing alkyl radicals containing in the range of about 3 up to 20 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl radicals further bearing one or more substituents as set forth above.

As employed herein, "cycloalkenyl" refers to ring-containing alkenyl radicals having at least one carbon-carbon double bond in the ring, and having in the range of about 3 up to 20 carbon atoms, and "substituted cycloalkenyl" refers to cyclic alkenyl radicals further bearing one or more substituents as set forth above.

As employed herein, "cycloalkynyl" refers to ring-containing alkynyl radicals having at least one carbon-carbon triple bond in the ring, and having in the range of about 3 up to 20 carbon atoms, and "substituted cycloalkynyl" refers to cyclic alkynyl radicals further bearing one or more substituents as set forth above.

As employed herein, "aryl" refers to mononuclear and polynuclear aromatic radicals having in the range of 6 up to 14 carbon atoms, and "substituted aryl" refers to aryl radicals further bearing one or more substituents as set forth above, for example, alkylaryl moieties.

As employed herein, "heterocycle" refers to ring-containing radicals having one or more heteroatoms (*e.g.*, N, O, S) as part of the ring structure, and having in the range of 3 up to 20 atoms in the ring. Heterocyclic moieties may be saturated or unsaturated when optionally containing one or more double bonds, and may contain more than one ring. Heterocyclic moieties include, for example, monocyclic moieties such as imidazolyl moieties, pyrimidinyl moieties, isothiazolyl moieties, isoxazolyl moieties, moieties, and the like, and bicyclic heterocyclic moieties such as azabicycloalkanyl moieties, oxabicycloalkyl moieties, and the like. The term "substituted heterocycle" refers to heterocycles further bearing one or more substituents as set forth above.

As employed herein, "azo" refers to the bivalent moiety –N=N–, wherein each single bond is attached to a different carbon atom.

As employed herein, "halogen" refers to fluoride, chloride, bromide or iodide radicals.

In accordance with the present invention, A is a 5-, 6- or 7-membered unsaturated heterocyclic moiety, containing a ring having at least one nitrogen atom located on the ring in a position adjacent to a carbon atom which bears a linking moiety as a substituent. The ring further contains 3, 4 or 5 independently variable atoms selected from carbon, nitrogen, sulfur and oxygen. Thus, A can be pyridinyl, imidazolyl, pyridazinyl, pyrimidinyl, pyrazoyl, pyrazinyl, triazolyl, triazinyl, tetrazolyl, tetrazinyl, isoxazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, oxadiazinyl, isothiazolyl, thiazoyl, dioxazolyl, oxathiazolyl, oxathiazinyl, azepinyl, diazepinyl, and the like. Those of skill in the art will recognize that multiple isomers exist for a single chemical formula; each of the possible isomeric forms of the various empirical formulae set forth herein are contemplated by the invention. When a variable ring atom is carbon, it bears a hydrogen, or is optionally substituted with halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, thiol, nitro, carboxyl, ester, cyano, amine, amide, carboxamide, amidine, amido, sulfonamide, and the like, with presently preferred embodiments having no substituent (*i.e.*, q is 0) or bearing the following substituents: halogen, alkyl, containing one up to four carbon atoms, fluorinated alkyl, containing one up to four carbon atoms, aryl, and amine. Substitution at position Z of the ring is presently preferred.

In accordance with one embodiment of the invention, A is a 5-, 6- or 7-membered ring containing, as ring members, a nitrogen atom and a sulfur atom. Moieties contemplated for use by this embodiment of the invention include those wherein A is isothiazol-3-yl (1,2-thiazol-3-yl), thiazol-4-yl (1,3,-thiazol-4-yl), thiazol-2-yl (1,3-thiazol-2-yl), 1,2-thiazin-3-yl, 1,3-thiazin-4-yl, 1,4-thiazin-3-yl, 1,3-thiazin-2-yl, thiazepinyl, and the like. Presently preferred moieties include those wherein A is isothiazol-3-yl (1,2-thiazol-3-yl), thiazol-4-yl (1,3-thiazol-4-yl) and thiazol-2-yl (1,3-thiazol-2-yl).

In accordance with another embodiment of the invention, A is a 5-, 6- or 7-membered ring containing, as ring members, a nitrogen atom and an oxygen atom. Moieties contemplated by this

embodiment of the invention include those wherein A is 1,2-oxazin-3-yl, 1,3-oxazin-4-yl, 1,4-oxazin-3-yl, 1,3-oxazin-2-yl, oxazol-2-yl, isoxazol-3-yl, oxazol-4-yl, oxazepinyl, and the like. Presently preferred moieties include those wherein A is oxazol-2-yl, isoxazol-3-yl and oxazol-4-yl.

In accordance with another embodiment of the invention, A is a 5-, 6- or 7-membered ring containing, as a ring member, a nitrogen atom. Moieties contemplated by this embodiment of the invention include those wherein A is 2-pyridinyl and 2-pyrrolyl.

In accordance with another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, two nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 3-pyridazinyl (1,2-diazin-3-yl), pyrimidin-4-yl (1,3-diazin-4-yl), pyrazin-3-yl (1,4-diazin-3-yl), pyrimidin-2-yl (1,3-diazin-2-yl), pyrazol-3-yl (1,2-diazol-3-yl), imidazol-4-yl (1,3-isodiazol-4-yl, imidazol-2-yl (1,3-isodiazol-2-yl), diazepinyl, and the like. Presently preferred moieties include those wherein A is 3-pyridazinyl (1,2-diazin-3-yl), pyrimidin-4-yl (1,3-diazin-4-yl), pyrazin-3-yl (1,4-diazin-3-yl), pyrimidin-2-yl (1,3-diazin-2-yl), 1,3-isodiazol-4-yl and 1,3-isodiazol-2-yl.

In accordance with still another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, three nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 1,2,3-triazin-4-yl, 1,2,4-triazin-6-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,3,5-triazin-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, triazepinyl, and the like. Presently preferred moieties include those wherein A is 1,2,3-triazin-4-yl, 1,2,4-triazin-6-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,3,5-triazin-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl.

In accordance with still another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, four nitrogen atoms. Moieties contemplated for use in the practice of the invention include those wherein A is tetrazin-2-yl, tetrazin-3-yl, tetrazin-5-yl, tetrazolyl, tetrazepinyl, and the like. Presently preferred moieties include those wherein A is tetrazolyl.

In accordance with yet another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, one sulfur atom and two nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 1,2,6-thiadiazin-3-yl, 1,2,5-thiadiazin-3-yl, 1,2,4-thiadiazin-3-yl, 1,2,5-thiadiazin-4-yl, 1,2,3-thiadiazin-4-yl, 1,3,4-thiadiazin-5-yl, 1,3,4-thiadiazin-2-yl, 1,2,4-thiadiazin-5-yl, 1,3,5-thiadiazin-4-yl, 1,3,5-thiadiazin-2-yl, 1,2,4-thiadiazol-3-yl, 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2,5-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, thiadiazepinyl, and the like. Presently preferred moieties include those wherein A is 1,2,4-thiadiazol-3-yl, 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2,5-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl.

In accordance with yet another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, one oxygen atom and two nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 1,2,6-oxadiazin-3-yl, 1,2,5-oxadiazin-3-yl, 1,2,4-oxadiazin-3-yl, 1,2,5-oxadiazin-4-yl, 1,2,3-oxadiazin-4-yl, 1,3,4-oxadiazin-5-yl, 1,3,4-oxadiazin-2-yl, 1,2,4-oxadiazin-5-yl, 1,3,5-oxadiazin-4-yl, 1,3,5-oxadiazin-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,3-oxadiazol-4-yl, 1,3,4-oxadiazol-2-yl, 1,2,5-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, oxadiazepinyl, and the like. Presently preferred moieties include those wherein A is 1,2,4-oxadiazol-3-yl, 1,2,3-oxadiazol-4-yl, 1,3,4-oxadiazol-2-yl, 1,2,5-oxadiazol-3-yl and 1,2,4-oxadiazol-5-yl.

In accordance with still another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing as ring members, one up to six nitrogen atoms, and/or one up to six carbon atoms, and/or zero up to five sulfur atoms, and/or zero up to five oxygen atoms.

Further, in accordance with the present invention, L is a linking moiety which links moieties A and B. L is selected from substituted or unsubstituted alkenylene moieties, alkynylene moieties or azo moieties. Presently preferred compounds of the invention are those wherein L is alkenylene or alkynylene moieties containing two carbon atoms, with alkynylene most preferred.

Further, in accordance with the present invention, B is a moiety linked through bridging moiety L to moiety A. Radicals contemplated for use in the invention are those wherein B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, substituted or unsubstituted aryl, and the like.

Presently preferred compounds of the invention are those wherein B is a substituted or unsubstituted hydrocarbyl selected from substituted or unsubstituted alkyl moieties, alkenyl moieties, dialkenyl moieties, trialkenyl moieties, alkynyl moieties, alkadiynyl moieties, alkatriynyl moieties, alkenynyl moieties, alkadienynyl moieties, alkenediynyl moieties, and the like.

Further preferred compounds of the invention are those wherein B is a substituted or unsubstituted cyclohydrocarbyl selected from substituted or unsubstituted cycloalkyl moieties, cycloalkenyl moieties, cycloalkadienyl moieties, cycloalkatrienyl moieties, cycloalkynyl moieties, cycloalkadiynyl moieties, bicyclic hydrocarbon moieties wherein two rings have two atoms in common, and the like. Especially preferred compounds are those wherein B is cycloalkyl and cycloalkenyl having in the range of 4 up to about 8 carbon atoms. Exemplary compounds include cyclopropanyl, cyclopentenyl and cyclohexenyl. Also especially preferred are bicyclic hydrocarbon moieties wherein two rings have two atoms in common; exemplary compounds include indenyl, dihydroindenyl, naphthalenyl and dihydronaphthalenyl.

Still further preferred compounds of the invention are those wherein B is a substituted or unsubstituted heterocycle, optionally containing one or more double bonds. Exemplary compounds include pyridyl, thiazolyl, furyl, dihydropyranyl, dihydrothiopyranyl, piperidinyl, isoxazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like. Also preferred are compounds wherein B is substituted or unsubstituted aryl. Especially preferred compounds are those wherein substituents are aryl and heterocycle, optionally bearing further substituents as described herein, methyl, trifluoromethyl, cyclopropyl, alkoxy, halogen and cyano. Also preferred are compounds wherein B is a bicylic heterocyle moiety wherein two rings have two atoms in common. Exemplary compounds include indolyl and isoquinolinyl.

Those of skill in the art recognize that invention compounds may contain one or more chiral centers, and thus can exist as racemic mixtures. For many applications, it is preferred to carry out stereoselective syntheses and/or to subject the reaction product to appropriate purification steps so as to produce substantially optically pure materials. Suitable stereoselective synthetic procedures for producing optically pure materials are well known in the art, as are procedures for purifying racemic mixtures into optically pure fractions. Those of skill in the art will further recognize that invention compounds may exist in polymorphic forms wherein a compound is capable of crystallizing in different forms. Suitable methods for identifying and separating polymorphisms are known in the art.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, esterified carboxy is, for example, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl or phenyl-lower alkoxycarbonyl substituted in the phenyl moiety by one or more substituents selected from lower alkyl, lower alkoxy, halo and halo-lower alkyl. Esterified carboxy-lower-alkoxy is, for example, lower alkoxycarbonyl-lower alkoxy. Amidated carboxy is, for example, unsubstituted or aliphatically substituted carbamoyl such as carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-phenyl- or N-lower-alkyl-N-phenyl-carbamoyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, acyl is, for example, lower alkanoyl, lower alkenoyl or unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted benzoyl. Acylamino is, for example, lower alkanoylamino, and N-acyl-N-lower alkylamino is, for example, N-lower alkanoyl-N-lower-alkylamino or unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted benzoylamino.

As referred to in reference to compounds excluded herein when referring to novel compounds of the invention, "lower" groups are understood to comprise up to and including seven carbon atoms. N-lower-alkyl-N-phenylcarbamoyl is, for example, N-C_1-C_4alkyl-N-phenylcarbamoyl, such as N-methyl, N-ethyl, N-propyl, N-isopropyl or N-butyl-N-phenylcarbamoyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, amino-lower alkyl is, for example, amino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-NH_2 in which n is 2 or 3, such as aminomethyl, 2-aminoethyl, 3-aminopropyl or 4-aminobutyl. Hydroxy-lower alkyl is, for example, hydroxy-C_1-C_4alkyl, such as hydroxymethyl, 2-hydroxy ethyl, 3-hydroxypropyl, 2-hydroxyisopropyl or 4-hydroxybutyl. Halo-lower alkyl is, for example, polyhalo-C_1-C_4alkyl, such as trifluoromethyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, lower alkoxy is, for example, C_1-C_7alkoxy, preferably C_1-C_4alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy or butyloxy, but may also represent isobutyloxy, sec.butyloxy, tert.-butyloxy or a C_5-C_7alkoxy group, such as a pentyloxy, hexyloxy or heptyloxy group.amino-lower alkoxy is, for example, amino-C_2-C_4alkoxy preferably of the formula -O-$(CH_2)_n$-NR_aR_b in which n is 2 or 3, such as 2-aminoethoxy, 3-aminopropyloxy or 4-aminobutyloxy. Carboxy-lower-alkoxy is, for example, carboxy-C_1-C_4alkoxy, such as carboxymethoxy, 2-carboxyethoxy, 3-carboxypropyloxy or 4-carboxybutyloxy. Lower alkanoyloxy is, for example, C_1-C_7alkanoyloxy, such as acetoxy, propionyloxy, butyryloxy, isobutyryloxy or pivaloyloxy. Halo-lower alkoxy is, for example, halo- or polyhalo-C_1-C_7alkoxy, preferably halo- or polyhalo-C_1-C_4alkoxy, such as halo- or polyhaloethoxy, halo- or polyhalopropyloxy or butyl-oxy, wherein "poly" refers, for example, to tri- or pentahalo, and "halo" denotes, for example, fluoro or chloro.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, lower alkylamino-lower alkoxy is, for example, C_1-C_4alkylamino-C_2-C_4alkoxy, preferably of the formula -O-(CH_2)n-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups as defined hereinbefore, such as methyl, ethyl, propyl or butyl. Lower alkylamino-lower alkyl is, for example, C_1-C_4alkylamino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups as defined hereinbefore, such as methyl, ethyl, propyl or butyl. Di-lower alkylamino-lower alkyl is, for example, Di-C_1-C_4alkylamino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups such as methyl, ethyl, propyl or butyl. Di-lower alkylamino-lower alkoxy is, for example, Di-C_1-C_4alkylamino-C_2-C_4alkoxy, preferably of the formula -O-$(CH_2)_n$-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups such as methyl, ethyl, propyl or butyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, optionally hydroxy-substituted lower alkyleneamino-lower alkyl is, for example, unsubstituted or hydroxy-substituted 5- to 7-membered alkyleneamino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-R_c in which n is 2 or 3 and R_c pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, homopiperidino or hydroxyhomopiperidino. Furthermore, optionally hydroxy-

substituted lower alkyleneamino-lower alkoxy is, for example, unsubstituted or hydroxy-substituted 5- to 7-membered alkyleneamino-C_1-C_4alkoxy, preferably of the formula -O-$(CH_2)_n$-R_c in which n is 2 or 3 and R_c pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, homopiperidino or hydroxyhomopiperidino.

In accordance with another embodiment of the present invention, there are provided pharmaceutical compositions comprising heterocyclic compounds as described above, in combination with pharmaceutically acceptable carriers. Optionally, invention compounds can be converted into non-toxic acid addition salts, depending on the substituents thereon. Thus, the above-described compounds (optionally in combination with pharmaceutically acceptable carriers) can be used in the manufacture of medicaments useful for the treatment of a variety of indications.

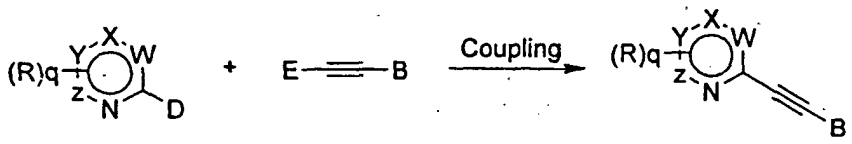
Pharmaceutically acceptable carriers contemplated for use in the practice of the present invention include carriers suitable for oral, sublingual intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, intraoccular, intracranial, inhalation, rectal, vaginal, and the like administration. Administration in the form of creams, lotions, tablets, capsules, pellets, dispersible powders, granules, suppositoiries, syrups, elixirs, lozenges, injectable solutions, sterile aqueous or non-aqueous solutions, suspensions or emulsions, patches, and the like, is contemplated. Pharmaceutically acceptable carriers include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, dextrans, and the like.

Invention compounds can optionally be converted into non-toxic acid addition salts. Such salts are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. Representative salts include hydrochloride, hydrobromide, sulfate, bisulfate, methanesulfonate, acetate, oxalate, adipate, alginate, aspartate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, toluenesulfonate (tosylate), citrate, malate, maleate, fumarate, succinate, tartrate, napsylate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, benzenesulfonate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, glucoheptanoate, glycerophosphate, heptanoate, hexanoate, undecanoate, 2-hydroxyethanesulfonate,ethanesulfonate, and the like. Salts can also be formed with inorganic acids such as sulfate, bisulfate, hemisulfate, hydrochloride, chlorate, perchlorate, hydrobromide, hydroiodide, and the like. Examples of a base salt include ammonium salts; alkali metal salts such as sodium salts, potassium salts, and the like; alkaline earth metal salts such as calcium salts, magnesium salts, and the like; salts with organic bases such as dicyclohexylamine salts, *N*-methyl-D-glucamine, phenylethylamine, and the like; and salts with amino acids such as arginine, lysine, and the like. Such salts can readily be prepared employing methods well known in the art.

In accordance with another embodiment of the present invention, there are provided methods

for the preparation of heterocyclic compounds as described above. For example, many of the heterocyclic compounds described above can be prepared using synthetic chemistry techniques well known in the art (see *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. and Rees, C. W. eds., Pergamon Press, Oxford, 1984) from a precursor of the substituted heterocycle of Formula I as outlined in Scheme 1.

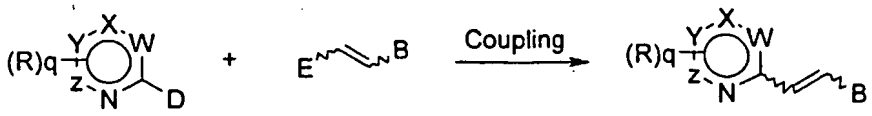
Scheme 1



Thus in Scheme 1, a substituted heterocycle precursor (prepared using synthetic chemistry techniques well known in the art) is reacted with an alkyne derivative. In Scheme 1, $(R)_q$, W, X, Y, Z and B are as defined above and D and E are functional groups which are capable of undergoing a transition metal-catalyzed cross-coupling reaction. For example, D is a group such as hydrogen, halogen, acyloxy, fluorosulfonate, trifluoromethanesulfonate, alkyl- or arylsulfonate, alkyl- or arylsulfinate, alkyl- or arylsulfide, phosphate, phosphinate, and the like, and E is hydrogen or a metallic or metalloid species such as Li, MgX (X is halogen), SnR_3, $B(OR)_2$, SiR_3, GeR_3, and the like. The coupling may be promoted by a homogeneous catalyst such as $PdCl_2(PPh_3)_2$, or by a heterogeneous catalyst such as Pd on carbon in a suitable solvent (*e.g.*, tetrahydrofuran (THF), dimethoxyethane (DME), acetonitrile, dimethylformamide (DMF), *etc.*). Typically, a co-catalyst such as copper (I) iodide and a base (*e.g.*, triethylamine, K_2CO_3 *etc.*) will also be present in the reaction mixture. The coupling reaction typically proceeds by allowing the reaction temperature to warm slowly from about 0° C up to ambient temperature over a period of several hours. The reaction mixture is then maintained at ambient temperature, or heated to a temperature anywhere between 30° C and 150° C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 48 hours, with about 12 hours typically being sufficient. The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like.

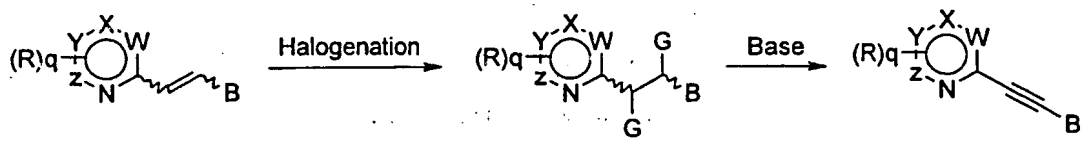
Another embodiment of the present invention is illustrated in Scheme 2. A substituted heterocycle precursor is reacted with an alkene derivative in a manner similar to the procedure described for Scheme 1.

Scheme 2



The alkene derivative product from Scheme 2 may be converted to an alkyne derivative using the approach outlined in Scheme 3.

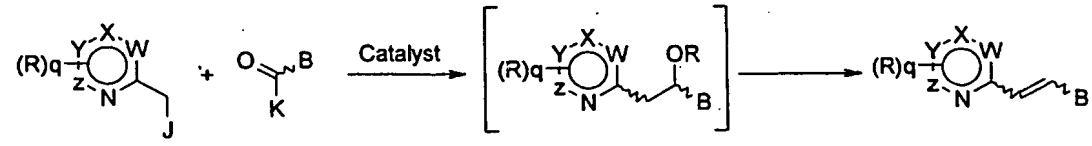
Scheme 3



Thus, the alkene derivative may be contacted with a halogenating agent such as chlorine, bromine, iodine, NCS (N-chlorosuccinimide), NBS (N-bromosuccinimide), NIS (N-iodosuccinimide), iodine monochloride, etc. in a suitable solvent (CCl_4, $CHCl_3$, CH_2Cl_2, acetic acid, and the like). The resulting halogenated derivative (G = halogen) is then treated with a suitable base such as NaOH, KOH, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (diazabicyclononene), DABCO (1,4-diazabicyclo[2.2.2]octane), and the like, which promotes a double elimination reaction to afford the alkyne. The reaction is carried out in a suitable solvent such as ethanol, acetonitrile, toluene, *etc.* at an appropriate temperature, usually between about 0° C and 150° C.

In another embodiment of the present invention, a substituted heterocyclic derivative is reacted with an aldehyde or ketone to provide a substituted alkene. (See Scheme 4.)

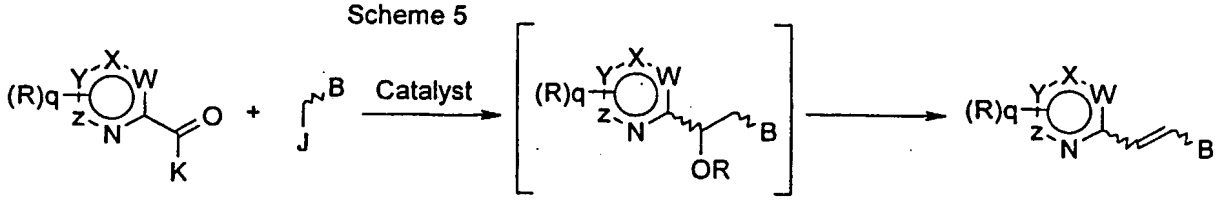
Scheme 4



Thus, in Scheme 4, J is hydrogen, PR_3, $P(O)(OR)_2$, SO_2R, SiR_3, and the like, K is hydrogen, alkyl or aryl (as defined previously) and R is hydrogen, acetyl, and the like. Suitable catalysts for this reaction include bases such as NaH, *n*-buytllithium, lithium diisopropylamide, lithium hexamethyl disilazide, H_2NR, HNR_2, NR_3 *etc.*, or electropositive reagents such as Ac_2O, $ZnCl_2$, and the like. The reaction is carried out in a suitable solvent (THF, acetonitrile, *etc.*) at an appropriate temperature, usually between about 0° C and 150° C. Sometimes an intermediate is isolated and purified or partially purified before continuing through to the alkene product.

In yet another embodiment of the present invention, a substituted heterocyclic aldehyde or ketone is reacted with an activated methylene-containing compound to provide a substituted alkene. (See Scheme 5.)

Scheme 5

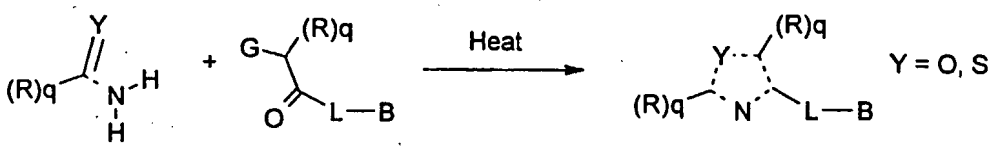


Thus, in Scheme 5, J, K, R, the catalyst and reaction conditions are as described for Scheme 4. Again, as in Scheme 4, sometimes an intermediate is isolated and purified or partially purified before continuing through to the alkene product.

The alkene products from the reactions in Scheme 4 and Scheme 5 may be converted to an alkyne derivative using reagents and conditions as described for Scheme 3.

Another method for the preparation of heterocyclic compounds of Formula I is depicted in Scheme 6.

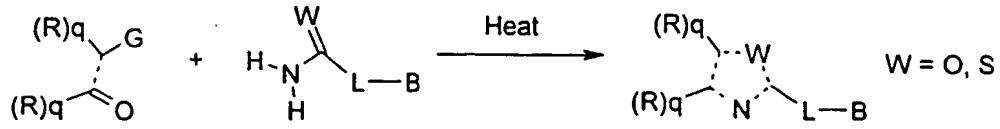
Scheme 6



In scheme 6, Y is O or S and G is halogen or a similar leaving group, and L and B are as defined previously. The reagents are contacted in a suitable solvent such as ethanol, DMF, and the like and stirred until the product forms. Typically reaction temperatures will be in the range of ambient through to about 150° C, and reaction times will be from about 1 h to about 48 h, with about 70° C and 4 h being presently preferred. The heterocycle product can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like. Often, the product will be isolated as the hydrochloride or hydrobromide salt, and this material may be carried onto the next step with or without purification.

Yet another method for the preparation of heterocyclic compounds of Formula I is depicted in Scheme 7.

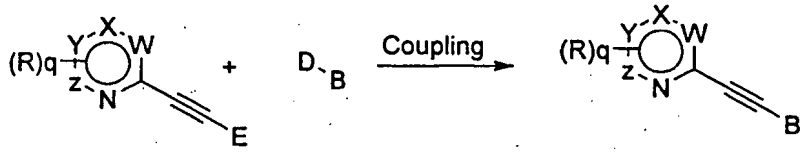
Scheme 7



In Scheme 7, W may be O or S, G is halogen or a similar leaving group, and L and B are as defined previously. The reaction conditions and purification procedures are as described for Scheme 6.

In another embodiment of the present invention, depicted in Scheme 8, an alkynyl-substituted heterocycle precursor (prepared using synthetic chemistry techniques well known in the art) is reacted with a species B, bearing a reactive functional group D (See Scheme 8.)

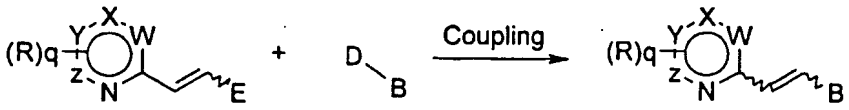
Scheme 8



In Scheme 8, $(R)_q$, W, X, Y, Z and B are as defined above and D and E are functional groups which are capable of undergoing a transition metal-catalyzed cross-coupling reaction. For example, D is a group such as hydrogen, halogen, acyloxy, fluorosulfonate, trifluoromethanesulfonate, alkyl- or arylsulfonate, alkyl- or arylsulfinate, alkyl- or arylsulfide, phosphate, phosphinate, and the like, and E is hydrogen or a metallic or metalloid species such as Li, MgX (X is halogen), SnR_3, $B(OR)_2$, SiR_3, GeR_3, and the like. The coupling may be promoted by a homogeneous catalyst such as $PdCl_2(PPh_3)_2$, or by a heterogeneous catalyst such as Pd on carbon in a suitable solvent (*e.g.* tetrahydrofuran (THF), dimethoxyethane (DME), acetonitrile, dimethylformamide (DMF), *etc.*). Typically a co-catalyst such as copper (I) iodide and the like and a base (*e.g.* triethylamine, K_2CO_3, *etc.*) will also be present in the reaction mixture. The coupling reaction is typically allowed to proceed by allowing the reaction temperature to warm slowly from about 0° C up to ambient temperature over a period of several hours. The reaction mixture is then maintained at ambient temperature, or heated to a temperature anywhere between about 30° C up to about 150° C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to about 48 hours, with about 12 hours typically being sufficient. The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like.

Another embodiment of the present invention is illustrated in Scheme 9.

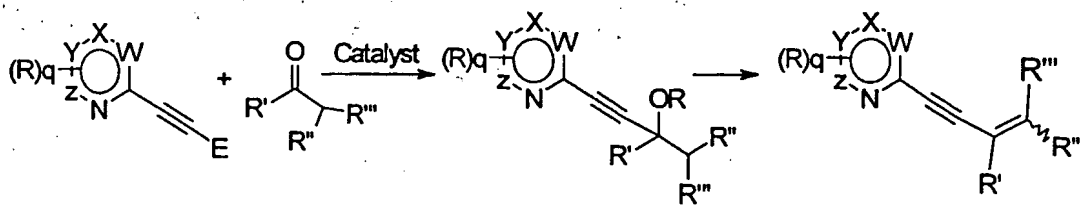
Scheme 9



An alkenyl-substituted heterocycle precursor is reacted with an alkene derivative in a manner similar to the procedure described for Scheme 8. The product alkene derivative from Scheme 9 may be converted to an alkyne derivative using the approach outlined previously in Scheme 3 above.

In yet another embodiment of the present invention, depicted in Scheme 10, an alkynyl-substituted heterocycle precursor is reacted with a species composed of a carbonyl group bearing substituents R' and CHR''R'''.

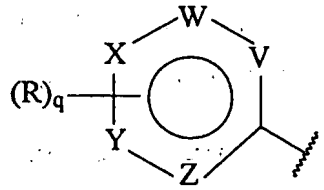
Scheme 10



Thus in Scheme 10, R', R'' and R''' may be hydrogen or other substituents as described previously, or may optionally combine to form a ring (this portion of the molecule constitutes B in the final compound). E is hydrogen or a metallic or metalloid species such as Li, MgX, wherein X is halogen, SnR_3, $B(OR)_2$, SiR_3, GeR_3, and the like. Suitable catalysts for this reaction include bases such as NaH, *n*-butyllithium, lithium diisopropylamide, lithium hexamethylsilazide, H_2NR, HNR_2, NR_3, nBu_4NF, ethylmagnesium halide, *etc.* R in Scheme 10 may be hydrogen, Ac, and the like. Typically the reaction is carried out in a suitable solvent such as diethylether, THF, DME, toluene, and the like, and at an appropriate temperature, usually between –100° C and 25° C. The reaction is allowed to proceed for an appropriate length of time, usually from about 15 minutes to about 24 hours. The intermediate bearing the -OR group may be isolated and purified as described above, partially purified or carried on to the next step without purification. Elimination of the –OR group to provide the alkene derivative may be accomplished using a variety of methods well known to those skilled in the art. For example, the intermediate may be contacted with $POCl_3$ in a solvent such as pyridine and stirred at a suitable temperature, typically between about 0° C and about 150° C, for an appropriate amount of time, usually between about 1 h and about 48 h. The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like.

In accordance with another embodiment of the present invention, there are provided methods of modulating the activity of excitatory amino acid receptors, said method comprising contacting said receptors with at least one compound as described above, as well as additional compounds of the same basic structure but having substitution patterns which may have been previously disclosed but never contmplated for use for such purposes. Thus, compounds contemplated for use in accordance with invention modulations methods include those having the structure **A—L—B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, in an amount sufficient to modulate the activity of said excitatory amino acid receptor, wherein:

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of **V, W, X, Y** and **Z** is $(CR)_p$, wherein p is 0, 1 or 2;

at least one of **V, W, X, Y** and **Z** is O, N or S;

the remainder of **V, W, X, Y** and **Z** are each independently O, N or S; and

each **R** is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded:

the compounds wherein A is a 6-membered ring wherein:

V, W, X and **Y** are (CR)p, wherein p is 1,

Z is N;

R at the V position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at

the W position is hydrogen; R at the X position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Y position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo, and

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents.

As employed herein, "excitatory amino acid receptors" refers to a class of cell-surface receptors which are the major class of excitatory neurotransmitter receptors in the central nervous system. In addition, receptors of this class also mediate inhibitory responses. Excitatory amino acid receptors are membrane spanning proteins that mediate the stimulatory actions of the amino acid glutamate and possibly other endogenous acidic amino acids. Excitatory amino acids are crucial for fast and slow neurotransmission and they have been implicated in a variety of diseases including Alzheimer's disease, stroke, schizophrenia, head trauma, epilepsy, and the like. In addition, excitatory amino acids are integral to the processes of long-term potentiation and depression which are synaptic mechanisms underlying learning and memory. There are three main subtypes of excitatory amino acid receptors: (1) the metabotropic receptors; (2) the ionotropic NMDA receptors; and (3) the non-NMDA receptors, which include the AMPA receptors and kainate receptors.

As employed herein, the phrase "modulating the activity of" refers to altered levels of activity so that the activity is different with the use of the invention method when compared to the activity without the use of the invention method. Modulating the activity of excitatory amino acid receptors includes the suppression or augmentation of the activity of receptors. Suppression of receptor activity may be accomplished by a variety of means, including blocking of a ligand binding site, biochemical and/or physico-chemical modification of a ligand binding site, binding of agonist recognition domains, preventing ligand-activated conformational changes in the receptor, preventing the activated receptor from stimulating second messengers such as G-proteins, and the like. Augmentation of receptor activity may be accomplished by a variety of means including, stabilization of a ligand binding site, biochemical and/or physico-chemical modification of a ligand binding site, binding of agonist recognition domains, promoting ligand-activated conformational changes in the receptor, and the like.

Excitatory amino acid receptor activity can be involved in numerous disease states. Therefore modulating the activity of receptors also refers to a variety of therapeutic applications, such as the treatment of cerebral ischemia, chronic neurodegeneration, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of respiration, motor control and function, attention deficit disorders, concentration disorders, pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, eating disorders, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia or astroytomas, and the like.

The compounds contemplated for use in accordance with of invention modulatory methods are especially useful for the treatment of mood disorders such as anxiety, depression, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, and the like; disorders of extrapyramidal motor function such as Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, tardive dyskinesia, and the like.

Compounds contemplated for use in accordance with invention modulatory methods are also especially useful for the treatment of pain disorders such as neuropathic pain, chronic pain, acute pain, painful diabetic neuropathy, post-herpetic neuralgia, cancer-associated pain, pain associated with chemotherapy, pain associated with spinal cord injury, pain associated with multiple sclerosis, causalgia and reflex sympathetic dystrophy, phantom pain, post-stroke (central) pain, pain associated with HIV or AIDS, trigeminal neuralgia, lower back pain, myofacial disorders, migraine, osteoarthritic pain, postoperative pain, dental pain, post-burn pain, pain associated with systemic lupus, entrapment neuropathies, painful polyneuropathies, ocular pain, pain associated with inflammation, pain due to tissue injury, and the like.

"Contacting" may include contacting in solution or in solid phase.

"Pharmaceutically acceptable salt" refers to a salt of the compound used for treatment which possesses the desired pharmacological activity and which is physiologically suitable. The salt can be formed with organic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, heptanoate, hexanoate, 2-hydroxyethanesulfonate, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, tartrate, toluenesulfonate, undecanoate, and the like. The salt can also be formed with inorganic acids such as sulfate, bisulfate, chlorate, perchlorate, hemisulfate, hydrochloride, hydrobromide, hydroiodide, and the like. In addition, the salt can be formed with a base salt, including

ammonium salts, alkali metal salts such as sodium salts, potassium salts, and the like; alkaline earth metal salts such as calcium salts, magnesium salts, and the like; salts with organic bases such as dicyclohexylamine salts, *N*-methyl-D-glucamine, phenylethylamine, and the like; and salts with amino acids such as arginine, lysine, and the like.

Salt forms of compounds herein find several advantages. Certain pharmaceutically acceptable salt forms of heterocyclic compounds described herein, achieve higher solubility as compared with non-salt forms. In addition, certain salt forms are more compatible with pharmaceutical uses. For example, the hydrochloric acid salt of 2-(phenylethynl)-1,3-thiazole is an oil while the toluene sulfonic acid salt form of 2-(phenylethynl)-1,3-thiazole is a solid that is soluble in aqueous medium. (See Example 187.) Characteristics of salt forms of compounds depend on the characteristics of the compound so treated, and on the particular salt employed.

In accordance with another embodiment of the invention, there are provided methods of modulating the activity of metabotropic glutamate receptors, said method comprising contacting metabotropic glutamate receptors with a concentration of a heterocylic compound as described above in accordance with invention methods for modulating the acitivity of excitatory amino acid receptors, sufficient to modulate the activity of said metabotropic glutamate receptors.

As used herein, the phrase "metabotropic glutamate receptor" refers to a class of cell-surface receptors which participates in the G-protein-coupled response of cells to glutamatergic ligands. Three groups of metabotropic glutamate receptors, identified on the basis of amino acid sequence homology, transduction mechanism and binding selectivity are presently known and each group contains one or more types of receptors. For example, Group I includes metabotropic glutamate receptors 1 and 5 (mGluR1 and mGluR5), Group II includes metabotropic glutamate receptors 2 and 3 (mGluR2 and mGluR3) and Group III includes metabotropic glutamate receptors 4, 6, 7 and 8 (mGluR4, mGluR6, mGluR7 and mGluR8). Several subtypes of each mGluR type may be found; for example, subtypes of mGluR1 include mGluR1a, mGluR1b and mGluR1c.

In accordance with another embodiment of the invention, there are provided methods of treating a wide variety of disease conditions, said method comprising administering to a patient having a disease condition a therapeutically effective amount of at least one of the heterocyclic compounds described above in accordance with invention methods for modulating the activity of excitatory amino acid receptors.

As used herein, "treating" refers to inhibiting or arresting the development of a disease, disorder or condition and/or causing the reduction, remission, or regression of a disease, disorder or condition. Those of skill in the art will understand that various methodologies and assays may be used to assess the development of a disease, disorder or condition, and similarly, various methodologies and assays may be used to assess the reduction, remission or regression of a disease, disorder or condition.

Disease conditions contemplated for treatment in accordance with the invention include cerebral ischemia, chronic neurodegeneration, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of respiration, motor control and function, attention deficit disorders, concentration disorders, pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, eating disorders, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia, astrocytomas, and the like.

Disease conditions contemplated for treatment in accordance with the present invention further include diseases of the pulmonary system, diseases of the nervous system, diseases of the cardiovascular system, diseases of the gastrointestinal system, diseases of the endocrine system, diseases of the exocrine system, diseases of the skin, cancer, diseases of the ophthalmic system, and the like.

As used herein, "administering" refers to means for providing heterocyclic compounds and/or salts thereof, as described herein, to a patient, using oral, sublingual intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, intraoccular, intracranial, inhalation, rectal, vaginal, and the like administration. Administration in the form of creams, lotions, tablets, capsules, pellets, dispersible powders, granules, suppositoiries, syrups, elixirs, lozenges, injectable solutions, sterile aqueous or non-aqueous solutions, suspensions or emulsions, patches, and the like, is also contemplated. The active ingredients may be compounded with non-toxic, pharmaceutically acceptable carriers including, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, dextrans, and the like.

For purposes of oral administration, tablets, capsules, troches, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, elixirs and lozenges containing various excipients such as calcium carbonae, lactose, calcium phosphate, sodium phosphate, and the like may be employed along with various granulating and disintegrating agents such as corn starch, potato starch, alginic acid, and the like, together with binding agents such as gum tragacanth, corn starch, gelatin, acacia, and the like. Lubricating agents such as magnesium stearate, stearic acid, talc, and the like may also be added. Preparations intended for oral use may be prepared according to any methods known to the art for the manufacture of pharmaceutical preparations and such preparations may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, saccharin, and the lake, flavoring agents such as peppermint, oil of wintergreen, and the like, coloring agents and preserving agents in order to provide pharmaceutically palatable preparations. Preparations for oral use may also contain suitable carriers include emulsions, solutions, suspensions, syrups, and the like, optionally containing additives such as wetting agents, emulsifying and suspending

agents, sweetening, flavoring and perfuming agents, and the like. Tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period of time.

For the preparation of fluids for parenteral administration, suitable carriers include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. For parenteral administration, solutions for the practice of the invention may comprise sterile aqueous saline solutions, or the corresponding water soluble pharmaceutically acceptable metal salts, as previously described. For parenteral administration, solutions of the compounds used in the practice of the invention may also comprise non-aqueous solutions, suspensions, emulsions, and the like. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile water, or some other sterile injectable medium immediately before use.

Aqueous solutions may also be suitable for intravenous, intramuscular, intrathecal, subcutaneous, and intraperitoneal injection. The sterile aqueous media employed are all readily obtainable by standard techniques well known to those skilled in the art. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, by heating the compositions, and the like. They can also be manufactured in the form of sterile water, or some other sterile medium capable of injection immediately before use.

Compounds contemplated for use in accordance with the present invention may also be administered in the form of suppositories for rectal or vaginal administration. These compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, and the like, such materials being solid at ambient temperatures but liquify and/or dissolve in internal cavities to release the drug.

The preferred therapeutic compositions for inocula and dosage will vary with the clinical indication. Some variation in dosage will necessarily occur depending upon the condition of the patient being treated, and the physician will, in any event, determine the appropriate dose for the individual patient. The effective amount of compound per unit dose depends, among other things, on the body weight, physiology, and chosen inoculation regimen. A unit dose of compound refers to the weight of compound without the weight of carrier (when carrier is used).

The route of delivery of compounds and compositions used for the practice of the invention is determined by the disease and the site where treatment is required. Since the pharmacokinetics and pharmacodynamics of compounds and compositions described herein will vary somewhat, the most preferred method for achieving a therapeutic concentration in a tissue is to gradually escalate the dosage and monitor the clinical effects. The initial dose, for such an escalating dosage regimen of therapy, will depend upon the route of administration.

In accordance with invention methods, the medicinal preparation can be introduced parenterally, by dermal application, and the like, in any medicinal form or composition. It is used as a solitary agent of medication or in combination with other medicinal preparations. Single and multiple therapeutic dosage regimens may prove useful in therapeutic protocols.

As employed herein, the phrase "a therapeutically effective amount", when used in reference to invention methods employing heterocyclic compounds and pharmaceutically acceptable salts thereof, refers to a dose of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated, the severity of the disorder, the activity of the specific compound used, the route of administration, the rate of clearance of the specific compound, the duration of treatment, the drugs used in combination or coincident with the specific compound, the age, body weight, sex, diet and general health of the patient, and like factors well known in the medical arts and sciences. Dosage levels typically fall in the range of about 0.001 up to 100 mg/kg/day; with levels in the range of about 0.05 up to 10 mg/kg/day being preferred.

In still another embodiment of the invention, there are provided methods for preventing disease conditions in a subject at risk thereof, said method comprising administering to said subject a therapeutically effective amount of at least one of the heterocyclic compounds described above in accordance with invention methods for modulating the activity of excitatory amino acid receptors.

As used herein, the phrase "preventing disease conditions" refers to preventing a disease, disorder or condition from occurring in a subject who may be at risk for the disease, but has not yet been diagnosed as having the disease. Those of skill in the art will understand that a variety of methods may be used to determine a subject at risk for a disease, and that whether a subject is at risk for a disease will depend on a variety of factors known to those of skill in the art, including genetic make-up of the subject, age, body weight, sex, diet, general health, occupation, exposure to environmental conditions, marital status, and the like, of the subject.

Those of skill in the art can readily identify a variety of assays that can be used to assess the activity of excitatory amino acid receptors. For receptor species that activate a second messenger

pathway, assays that measure receptor-activated changes in intracellular second messengers can be employed to monitor receptor activity. For example, inhibition of G-protein-coupled metabotropic glutamate receptors by antagonists can lead to inhibition of the glutamate-evoked increase in phosphatidylinositol (PI) hydrolysis, which can be assessed by measuring decreases in glutamate-stimulated products of PI hydrolysis. (See *e.g.*, Berridge *et al,* (1982) *Biochem. J.* 206:587-5950; and Nakajima *et al., J. Biol. Chem.* 267:2437-2442 (1992) and Example 23.) Similarly, activation of excitatory amino acid receptors that leads to the release of intracellular calcium or changes in intracellular calcium concentration can also be used to assess excitatory amino acid receptor activity. Methods of detection of transient increases in intracellular calcium concentration are well known in the art. (See *e.g.*, Ito *et al., J. Neurochem.* 56:531-540 (1991) and Example 22). Furthermore, for receptor species that mediate analgesia, assays that measure analgesic efficacy can be employed to monitor receptor activity (See Example 24).

The following examples are intended to illustrate but not to limit the invention in any manner, shape, or form, either explicitly or implicitly. While they are typical of those that might be used, other procedures, methodologies, or techniques known to those skill in the art may alternatively be used.

Example 1

Synthesis of 2-(1-Cyclohexen-1-ylethynyl)-1,3-thiazole

Triphenylphosphine (570 mg, 2.0 mmol) was dissolved in tetrahydrofuran (THF) (20 mL), then argon was bubbled through the solution for several minutes to deoxygenate it. Palladium(II) acetate (120 mg, 0.54 mmol) was added, and the reaction mixture was heated to 60°C for 0.5 h, and then cooled to ambient temperature. CuI (308 mg, 1.6 mmol), 2-bromo-1,3-thiazole (3.0 g, 18 mmol), 1-ethynylcyclohexene (2.4 g, 20 mmol), potassium carbonate (6 g, 45 mmol) and water (1.0 mL, 58 mmol) were dissolved in 50 mL dimethoxyether (DME) and argon was bubbled through the solution for several minutes to deoxygenate the mixture. The catalyst solution of triphenylphosphine and palladium (II) acetate in THF was added to the reaction flask which was heated to 75°C for 2h. After 2 h, heating was discontinued and the reaction was allowed to cool to ambient temperature. After stirring for 16 h, gas chromatography/mass spectrometry (GC/MS) analysis showed the reaction to be complete. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL) and washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 97:3 hexane:ethyl acetate to afford 2-(1-cyclohexen-1-ylethynyl)-1,3-thiazole (2.56 g, 74% yield) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J=3.0 Hz, 1H), 7.31 (d, J=3.0 Hz, 1H), 6.37-6.35 (m, 1H), 2.23-2.14 (m, 4H), 1.71-1.57 (m, 4H). MS (ESI) 190.0 (M^++H).

Example 2

Synthesis of 2-Methyl-4-(1,3-thiazol-2-yl)-3-butyn-2-ol

2-Bromo-1,3-thiazole (6.0 g, 37 mmol) and CuI (1.3 g, 7.3 mmol) were combined in DME (150 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (25 mL, 180 mmol) and $PdCl_2(PPh_3)_2$ (2.5 g, 3.7 mmol) were added and 2-methyl-3-butyne-2-ol (4.6 g, 55 mmol) was added dropwise. After stirring at ambient temperature for 16 h, GC/MS showed the reaction was not complete. The reaction was heated to reflux for 2 h. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (600 mL), washed with water (600 mL), brine (600 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 7:3 hexane:ethyl acetate to afford 4-(2-thiazolyl)-2-methyl-3-butyn-2-ol contaminated with 2,7-dimethyl-but-3,5-diyne-2,7-diol (the dimer of 2-methyl-3-butyne-2-ol). The product was crystallized from boiling hexane to afford 2-methyl-4-(1,3-thiazol-2-yl)-3-butyn-2-ol (2.18 g, 36% yield) as off white crystals that were contaminated with a small amount of 2,7-dimethyl-but-3,5-diyne-2,7-diol. M.p. 69-70°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J=3.0 Hz, 1H), 7.34 (d, J=3.0 Hz, 1H), 4.40 (s, 1H), 1.65 (s, 6H). MS (ESI) 168.1 (M^++H).

Example 3

Synthesis of 5-Chloro-3-pyridinyl trifluoromethanesulfonate

Trifluoromethanesulfonic anhydride (5.0 mL, 30 mmol) was dissolved in CH_2Cl_2 (100 mL), and cooled to 0°C 5-Chloro-3-pyridinol (3.10 g, 23.9 mmol), and triethylamine (6.5 mL, 47 mmol) were dissolved in CH_2Cl_2 (50 mL), and the resulting solution was added to the cold trifluoromethanesulfonic anhydride solution dropwise via cannula. The resulting dark brownish-red solution was stirred at 0°C for 5 minutes, and then the ice bath was removed and the reaction mixture was allowed to warm to ambient temperature. After stirring for 16 h at ambient temperature the reaction was quenched by pouring into water and basified by addition of saturated aqueous sodium carbonate. The basic aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), the combined organics were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting black viscous oil was filtered through a plug of silica gel and fractions were collected while eluting with 1:1 hexane:ethyl acetate. Fractions containing the desired product were combined, concentrated *in vacuo*, and further purified by column chromatography eluting with 15:1 then 10:1 hexane:ethyl acetate to afford 5-chloro-3-pyridinyl trifluoromethanesulfonate (3.68 g, 59% yield) as a golden liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J=2 Hz, 1H), 8.52 (d, J=2 Hz, 1H), 7.70 (t, J=3 Hz, 1H). MS (ESI) 261 (M^+, ^{35}Cl), 263 (M^+, ^{37}Cl).

Example 4

Synthesis of 3-Chloro-5-[(trimethylsilyl)ethynyl]pyridine

5-Chloro-3-pyridinyl trifluoromethanesulfonate (4.0 g, 15 mmol) and CuI (580 mg, 3.0 mmol) were combined in DME (100 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (10.6 mL, 76.5 mmol), and $PdCl_2(PPh_3)_2$ (1.1g, 1.5 mmol) were added, then trimethylsilyl-acetylene (3.3 ml, 23 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 1 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 99:1 hexane:ethyl acetate to afford 3-chloro-5-[(trimethylsilyl)ethynyl]pyridine (2.8 g, 87% yield) as a brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H), 8.44 (s, 1H), 7.70(s, 1H), 0.22 (s, 9H). MS (EI ionization) 209 (M^+).

Example 5

Synthesis of 3-Chloro-5-ethynylpyridine

3-Chloro-5-[(trimethylsilyl)ethynyl]pyridine (1.4g, 6.7mmol) was dissolved in methanol (15 ml) and cooled to 0°C, to the resulting solution was added potassium carbonate (93 mg, 0.67 mmol). The ice bath was removed and the reaction mixture was stirred at ambient temperature for 0.5 h at which time thin layer chromatography (TLC) and GC/MS analysis indicated that the reaction was complete. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether (50 mL), washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 3-chloro-5-ethynylpyridine (822mg, 90% yield) which was pure by GC/MS analysis. MS (EI ionization) 137 (^{35}Cl M^+), 139 (^{37}Cl M^+). This material was carried on to the next step without further purification.

Example 6

Synthesis of 3-Chloro-5-(1,3-thiazol-2-ylethynyl)pyridine

2-Bromo-1,3-thiazole (980 mg, 6.0 mmol) and CuI (230 mg, 1.2 mmol) were combined in DME (15 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (4.2 mL, 30 mmol) and $PdCl_2(PPh_3)_2$ (420 mg, 0.60 mmol) were added, then 3-chloro-5-ethynylpyridine (820 mg, 19 mmol) was added dropwise. After stirring at ambient temperature for 16 h, GC/MS analysis showed starting material remaining. The reaction mixture was heated at reflux for 2 h. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was

dissolved in ethyl acetate (100 mL), and washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 9:1 hexane:ethyl acetate to afford 3-chloro-5-(1,3-thiazol-2-ylethynyl)pyridine which contained some dimer. This material was crystallized from hot ethyl acetate to afford 3-chloro-5-(1,3-thiazol-2-ylethynyl)pyridine (300 mg 23% yield) as light orange crystals M.p. 124-125°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (d, J=1.5 Hz, 1H), 8.59 (d, J=3.0 Hz, 1H), 7.93 (d, J=3.0 Hz, 1H), 7.88 (t, J=2.0 Hz, 1H), 7.48 (d, J=3.0 Hz, 2H). MS (ESI) 221.1 (M^++H).

Example 7

Synthesis of 2-(Cyclohexylethynyl)-1,3-thiazole

2-Bromo-1,3-thiazole (3.1 g, 19 mmol) and CuI (290 mg, 1.5 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (13 mL, 95 mmol) and $PdCl_2(PPh_3)_2$ (530 mg, 0.76 mmol) were added and cyclohexylethyne (2.0 g, 19 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 99:1 hexane:ethyl acetate to afford 2-(cyclohexylethynyl)-1,3-thiazole (1.6 g, 44% yield) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, J=9.0 Hz, 1H), 7.28 (d, J=3.0 Hz, 1H), 2.68-2.59 (m, 1H), 1.91-1.28 (m, 10H). MS (ESI) 191.7 (M^+).

Example 8

Synthesis of 2-(1-Pentynyl)-1,3-thiazole

2-Bromo-1,3-thiazole (2.0 g, 12 mmol) and CuI (183 mg, 0.96 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8 mL, 60 mmol) and $PdCl_2(PPh_3)_2$ (337 mg, 0.48 mmol) were added and 1-pentyne (979 mg, 14.4 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 6 h at which time GC/MS analysis indicated that the reaction was not complete. Additional 1-pentyne (3.0 mL, 29 mmol) was added and the reaction was heated to 35°C under a condenser. After heating for 16 h, GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, 99:1, then 97:3 hexane:ethyl

acetate to 2-(1-pentynyl)-1,3-thiazole (820 mg, 44% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, J=3.0 Hz, 1H), 7.28 (d, J=3.0 Hz, 1H), 2.47-2.42 (m, 2H), 1.68-1.60 (m, 2H), 1.08 - 0.99 (m, 3H). MS (ESI) 151.6 (M^+).

Example 9

Synthesis of 2-(3-Cyclohexyl-1-propynyl)-1,3-thiazole

2-Bromo-1,3-thiazole (2.0 g, 12 mmol) and CuI (185 mg, 0.97 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8.5 mL, 61 mmol) and $PdCl_2(PPh_3)_2$ (340 mg, 0.49 mmol) were added and 3-cyclohexyl-1- propyne (2.9 g, 24 mmol) was added dropwise. The reaction was stirred at ambient temperature for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, then 98:2 hexane:ethyl acetate to afford 2-(3-cyclohexyl-1-propynyl)-1,3-thiazole (1.14 g, 46% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, J=3.0 Hz, 1H), 7.27 (d, J=3.0 Hz, 1H), 2.35 (d, J=6 Hz, 2H), 1.89-1.61 (m, 5H), 1.3 - 1.03 (m, 6H). MS (ESI) 205.9 (M^++H).

Example 10

Synthesis of 2-(1-Cyclohexen-1-ylethynyl)-5-nitro-1,3-thiazole

2-Bromo-5-nitro-1,3-thiazole (2.5 g, 12 mmol) and CuI (460 mg, 2.5 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8.4 mL, 60 mmol) and $PdCl_2(PPh_3)_2$ (840 mg, 1.2 mmol) were added and 1-ethynycyclohexene (1.5 g, 14.4 mmol) was added dropwise. The reaction was heated under reflux for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, 99:1 then 98.5:1.5 hexane:ethyl acetate to afford 2-(1-cyclohexen-1-ylethynyl)-5-nitro-1,3-thiazole (1.4 g, 51.8% yield) as a yellow powder. M.p. 85-86°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.5 (s, 1H), 6.52 (br s, 1H), 2.24 (br s, 4H), 1.63 (br s, 4H). MS (ESI) 235.1 (M^++H).

Example 11

Synthesis of 2-(3,3-Dimethyl-1-butynyl)-1,3-thiazole

Triphenylphosphine (380 mg, 1.5 mmol) was dissolved in THF (20 mL), then argon was bubbled through the solution for several minutes to deoxygenate it. Palladium(II) acetate (82 mg, 0.37 mmol) was added, and the reaction mixture was heated to 60°C for 0.5 h, and then cooled to ambient temperature. CuI (210 mg, 1.1 mmol), 2-bromo-1,3-thiazole (1.6 g, 9.8 mmol), potassium carbonate (4.2 g, 31 mmol) and water (0.70 mL, 39 mmol) were dissolved in DME (30 mL) and argon was bubbled through the mixture for several minutes to deoxygenate the mixture. 3,3-dimethyl-1-butyne (1.0 g, 12.2 mmol) was then added to mixture. The catalyst solution of triphenylphosphine and palladium (II) acetate in THF was added to the reaction flask which was heated to 30°C for 2h. After this time heating was discontinued and the mixture was allowed to stir at ambient temperature. After stirring for 16 h, GC/MS analysis showed the reaction to be complete. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, then 99:1 hexane:ethyl acetate to afford 2-(3,3-dimethyl-1-butynyl)-1,3-thiazole (0.45 g, 28% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, J=3.0 Hz, 1H), 7.28 (d, J=3.0 Hz, 1H), 1.33 (s, 9H). MS (ESI) 166.1 (M^++H).

Example 12

Synthesis of 1-(1,3-Thiazol-2-ylethynyl)cyclopentanol

2-Bromo-1,3-thiazole (3.1 g, 19 mmol) and CuI (360 mg, 1.9 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (13 mL, 94 mmol) and $PdCl_2(PPh_3)_2$ (660 mg, 0.94 mmol) were added and 1-ethynycyclopentanol (2.5 g, 23 mmol) was added dropwise. The reaction was heated at 50°C for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, 6:1 then 3:1 hexane:ethyl acetate to afford 1-(1,3-thiazol-2-ylethynyl)cyclopentanol (2.3 g, 52% yield) as a yellow powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J=3 Hz, 1H), 7.65 (d, J=3 Hz, 1H), 2.04-1.73 (m, 10.8H). MS (EI ionization) 193 (M^+).

Example 13

Synthesis of 2-(1-Cyclopenten-1-ylethynyl)-1,3-thiazole

1-(1,3-Thiazol-2-ylethynyl)cyclopentanol was dissolved in pyridine (20 ml) and phosphorus oxychloride (1.2 g, 6.2 mmol) was added dropwise under argon. The reaction was stirred at ambient temperature for 1h at which time a precipitate had appeared. At this time GC/MS analysis indicated that the reaction was complete and the pyridine was removed *in vacuo*. The residue was dissolved in ethyl acetate (200 mL) and washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 99:1 hexane:ethyl acetate to 2-(1-cyclopenten-1-ylethynyl)-1,3-thiazole (0.25 g, 24% yield) as a light brown solid. M.p. 70.5-72°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J=3.0 Hz, 1H), 7.34 (d, J=3.0Hz, 1H), 6.31-6.30 (m, 1H), 2.60-2.45 (m, 4H), 2.00-1.90 (m, 2H). MS (ESI) 176.1 (M^++H).

Example 14

Synthesis of Methyl 3-(1,3-thiazol-2-yl)-2-propynyl ether

2-Bromo-1,3-thiazole (2.0 g, 12 mmol) and CuI (456 mg, 2.4 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8.6 mL, 60 mmol) and $PdCl_2(PPh_3)_2$ (842 mg, 1.2 mmol) were added and methyl propargyl ether (1.00 g, 14.4 mmol) was added dropwise. The reaction was stirred at 55°C under a condenser. After stirring at 55°C for 16 h, GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, 99:1, 97:3, then 96:4 hexane:ethyl acetate to afford methyl 3-(1,3-thiazol-2-yl)-2-propynyl ether (250 mg, 13% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J=3.0 Hz, 1H), 7.37 (d, J=3.0 Hz, 1H), 4.37 (s, 2H), 3.47 (s, 3H). MS (ESI) 154.1 (M^++H).

Example 15

Synthesis of 2-Methyl-4-(3-pyridinyl)-3-butyn-2-ol

3-Bromopyridine (3.0 mL, 31 mmol), triethylamine (22 mL, 160 mmol), CuI (1.2 g, 6.2 mmol), and $PdCl_2(PPh_3)_2$ (1.1 g, 1.5 mmol) were combined in DME (92 mL) and cooled to 0°C. 2-Methyl-3-butyne-2-ol (9.0 mL, 93 mmol) was then added and the reaction was allowed to slowly warm to ambient temperature. The mixture was then heated to 55-60°C for 16 h. The mixture was filtered through Celite™, and the pad was washed thoroughly with ethyl acetate. The combined filtrates were washed with brine (3 x 100 mL), dried over $MgSO_4$, and filtered. The solution was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with 90:10 hexane:ethyl acetate

then ethyl acetate to afford 2-methyl-4-(3-pyridinyl)-3-butyn-2-ol (2.0 g, 40% yield) as a brown oil ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (br s, 1H), 8.52 (br s, 1H), 7.74-7.70 (m, 1H), 4.08 (br s, 1H), 1.63 (s, 3H). MS (EI ionization) 161 (M^+).

Example 16

Synthesis of 3-Ethynylpyridine

2-Methyl-4-(3-pyridinyl)-3-butyn-2-ol (611 mg, 3.79 mmol) was dissolved in toluene (12 mL) at ambient temperature. A small amount (spatula tip) of NaH (60% dispersion in mineral oil) was added, and the reaction was heated to reflux. After 15 minutes the reaction was cooled to ambient temperature, and quenched by the addition of 1M aqueous HCl (30 mL). Crude product from a previous preparation (~200 mg) was added to the workup mixture. The acidic aqueous was extracted with ethyl acetate (2 x 20 mL), basified by the addition of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude 3-ethynylpyridine (1.5 g, >100%) as a brown liquid.. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (br s, 1H), 8.58 (br s, 1H), 7.80-7.76 (m, 1H), 7.29-7.16 (m, 1H), 3.28 (s, 1H). A portion of this material was carried on to the next step without further purification.

Example 17

Synthesis of 3-(1,3-Thiazol-2-ylethynyl)pyridine

2-Bromo-1,3-thiazole (0.15 mL, 1.6 mmol), CuI (98 mg, o.51 mmol), $PdCl_2(PPh_3)_2$ (120 mg, 0.17 mmol) and triethylamine (2.8 mL, 20 mmol) were combined in DMF (6.8 mL) and cooled in an ice bath. 3-Ethynylpyridine (520 mg, 5.04 mmol) was then added to the mixture as a solution in DMF (3.0 mL). The ice bath was removed and the reaction was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered through a pad of Celite™, and the pad was washed thoroughly with ethyl acetate. The filtrate was washed with brine (3 x 20 mL). A partial emulsion was observed. The mixture was concentrated *in vacuo* and the residue was taken up in CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 80:20 followed by 30:20 hexane:ethyl acetate to afford 3-(1,3-thiazol-2-ylethynyl)pyridine (160 mg) as a mixture with another product exhibiting a mass of 204 in the GC/MS, assigned as pyridylalkyne dimer. A portion of the mixture (100 mg) was further purified by preparative reverse-phase HPLC eluting with a gradient of 80:20 to 0:100 water:acetonitrile over twenty minutes. The fractions containing the desired product were collected (detection by uv at 210 nm) to afford 3-(1,3-thiazol-2-ylethynyl)pyridine as a white waxy solid (15 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.3-8.5 (br s, 2 H), 7.92-7.90 (m, 2H), 7.50-7.30 (m, 2H). MS (ESI) 187.0 (M^++H).

Example 18

Synthesis of 3,3,5,5-Tetramethyl-1-(2-pyridinylethynyl)cyclohexanol

To a solution of 2-ethynylpyridine (1.0 g, 10 mmol) in THF at –78°C was added a 1.0 M solution of ethyl magnesium bromide in THF (10 mL, 10 mmol). After stirring at reduced temperature for 30 minutes a solution of 3,3,5,5-tetramethylcyclohexanone (1.5 g, 10 mmol) in THF was added rapidly. The mixture was allowed to warm to ambient temperature over 16 hours, then partitioned between water and ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resultant product was purified by flash column chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to afford 3,3,5,5-tetramethyl-1-(2-pyridinylethynyl)cyclohexanol (250 mg, 10% yield) as a white solid. M.p. 126-127°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.57 (m, 1H), 7.64 (m, 1H), 7.39 (d, J=5 Hz, 1H), 7.22 (m, 1H), 1.91 (d, J=9 Hz, 2H), 1.71 (d, J=9 Hz, 2H), 1.26 (s, 2H), 1.14 (s, 6H), 1.09 (s, 6H).

Example 19

Synthesis of 2-[(3,3,5,5-Tetramethyl-1-cyclohexen-1-yl)ethynyl]pyridine

3,3,5,5-Tetramethyl-1-(2-pyridinylethynyl)cyclohexanol (200 mg, 0.78 mmol) was dissolved in pyridine. $POCl_3$ (153 mg, 1.0 mmol) was added, and the mixture was heated to reflux for 6 h. After cooling, the $POCl_3$ and pyridine were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with 2:1 hexane:ethyl acetate to afford 2-[(3,3,5,5-tetramethyl-1-cyclohexen-1-yl)ethynyl]pyridine (148 mg, 80% yield) as a light tan solid. M.p. 55-56°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (m, 1H), 7.62 (m, 1H), 7.40 (d, J=7 Hz, 1H), 7.18 (m, 1H), 6.09 (s, 1H), 2.00 (s, 2H), 1.35 (s, 2H), 1.05 (s, 6H), 0.99 (s, 6H).

Example 20

Synthesis of 2-[(5-Methyl-1-cyclohexen-1-yl)ethynyl]pyridine and 2-[(3-methyl-1-cyclohexen-1-yl)ethynyl]pyridine (1:1)

Using the procedures for Examples 18 and 19 but with the appropriate starting materials, 2-[(5-methyl-1-cyclohexen-1-yl)ethynyl]pyridine and 2-[(3-methyl-1-cyclohexen-1-yl)ethynyl]pyridine were obtained as a mixture of racemic regioisomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (m, 1H), 7.62 (m, 1H), 7.40 (m, 1H), 7.19 (m, 1H), 6.32 (s, 0.5H), 6.20 (s, 0.5 H), 2.25 (m, 3H), 1.73 (m, 3H), 1.22 (m, 1H), 1.01 (m, 3H). MS (EI ionization) Two peaks: 197 (M^+).

Example 21

General procedure for 2-pyridylenynes

To a cooled a solution of 2-ethynylpyridine in THF to –78°C was added *n*-BuLi (1.6 M in hexane, 1 equiv). After 20 minutes stirring at reduced temperature this material was mixed with a solution of the appropriate ketone (1 equiv) in THF. The solution was allowed to warm slowly to ambient temperature. The reaction mixture was then quenched and partitioned between water and ethyl acetate. The organic layer was dried over Na_2SO_4; and concentrated *in vacuo*. The resultant product was purified by flash column chromatography on silica gel eluting with 1:1 hexane:ethyl acetate. The resulting product was dissolved in pyridine or a mixture of pyridine and methylene chloride (1:1). $POCl_3$ (1.2 equiv) was added and the solution refluxed for 4 to 8 hours. The resultant mixture was partitioned between 1M K_2CO_3 and ethyl acetate. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resultant product was purified by flash column chromatography on silica gel eluting with 2:1 hexane:ethyl acetate.

Using this general procedure the following invention compounds (see Examples 22-33) were obtained.

Example 22

Synthesis of 2-[(4-Methyl-1-cyclopenten-1-yl)ethynyl]pyridine and 2-[(3-Methyl-1-cyclopenten-1-yl)ethynyl]pyridine (1:1)

Reactants: 2-ethynylpyridine (620 mg, 6.0 mmol), 3-methylcyclopentanone (0.64 mL, 6.0 mmol); yields 2-[(4-methyl-1-cyclopenten-1-yl)ethynyl]pyridine and 2-[(3-methyl-1-cyclopenten-1-yl)ethynyl]pyridine (1:1) as a transparent oil (200 mg, 18% overall yield), as mixture of regio- and stereoisomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (m, 1H), 7.64 (m, 1H), 7.44 (m, 1H), 7.20 (m, 1H), 6.19 (m, 0.5H), 6.18 (m, 0.5H), 2.90 (m, 0.5H), 2.70 (m, 2.5H), 2.21 (m, 2H), 1.48 (m, 0.5H), 1.08 (app d, J= 7.5Hz, 3H). Two peaks: 182 (M^+), 167 (M^+-Me).

Example 23

Synthesis of 2-(Bicyclo[2.2.1]hept-2-en-2-ylethynyl)pyridine

Reactants: 2-ethynylpyridine (1.0 g, 10.0 mmol), norcamphor (1.1 g, 10.0 mmol); yields 2-(bicyclo[2.2.1]hept-2-en-2-ylethynyl)pyridine as a black oil (215 mg, 11% over two steps). This material was mixed with fumaric acid (128 mg, 1.11 mmol), dissolved in Methanol and the resulting solution was concentrated *in vacuo* to afford a dark brown solid. This was triturated with a mixture of ethyl acetate:ethanol (1:1) and the resultant solids were partitioned between aqueous K_2CO_3 and ethyl acetate. The organics were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with 2:1 hexane:ethyl acetate to afford 2-(bicyclo[2.2.1]hept-2-en-2-ylethynyl)pyridine (30 mg, 1.5 % overall yield) as a translucent brown oil.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (d, J= 5Hz, 1H), 7.64 (m, 1H), 7.40 (m, 1H), 7.19 (m, 1H), 6.48 (d, J=4Hz, 1H), 3.07 (s, 1H), 2.97 (s, 1H), 1.76 (m, 2H), 1.51 (m, 1H), 1.23 (m, 1H), 1.11 (m, 1H). MS (EI ionization) 195 (M^+).

Example 24

Synthesis of 2-[(2,6-Dimethyl-1-cyclohexen-1-yl)ethynyl]pyridine

Reactants: 2-ethynylpyridine (5.0 mmol, 515 mg), 2,6-dimethylcyclopentanone (6.0 mmol, 0.82 mL); yields 2-[(2,6-dimethyl-1-cyclohexen-1-yl)ethynyl]pyridine as a transparent oil (200 mg, 19% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (m, 1H), 7.60 (m, 1H), 7.42 (m, 1H), 7.19 (m, 1H), 2.40 (m, 1H), 2.10 (m, 2H), 2.01 (s, 3H), 1.76 (m, 2H), 1.56 (m, 1H), 1.34 (m, 1H), 1.22 (app d, J= 7 Hz, 3H). MS (EI ionization) 211 (M^+).

Example 25

Synthesis of 2-(1-Cyclohepten-1-ylethynyl)pyridine

Reactants: 2-ethynylpyridine (5.0 mmol, 515 mg), cycloheptanone (6.0 mmol, 0.71 mL); yields 2-(1-cyclohepten-1-ylethynyl)pyridine as a transparent oil (200 mg, 18% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (m, 1H), 7.59 (m, 1H), 7.40 (m, 1H), 7.16 (m, 1H), 6.52 (t, J= 7 Hz, 1H), 2.47 (m, 2H), 2.26 (m, 2H), 1.77 (s, 2H), 1.61 (m, 2H), 1.56 (m, 2H). MS (EI ionization) 197 (M^+).

Example 26

Synthesis of 2-(1-Cycloocten-1-ylethynyl)pyridine

Reactants: 2-ethynylpyridine (515 mg, 5.0 mmol), cyclooctanone (756 mg, 6.0 mmol); yields 2-(1-cycloocten-1-ylethynyl)pyridine as a transparent oil (250 mg, 24% overall yield).^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.62 (m, 1H), 7.40 (m, 1H), 7.18 (m, 1H), 6.33 (t, J= 7 Hz, 1H), 2.41 (m, 2H), 2.23 (m, 2H), 1.66 (s, 2H), 1.52 (br m, 6H). MS (EI ionization) 211 (M^+).

Example 27

Synthesis of 2-[(4-Methyl-1-cyclohexen-1-yl)ethynyl]pyridine

Reactants: 2-ethynylpyridine (6.0 mmol, 618 mg), 4-methylcyclohexanone (6.0 mmol, 672 mg); yields 2-[(4-methyl-1-cyclohexen-1-yl)ethynyl]pyridine as a transparent oil (250 mg, 21% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.59 (m, 1H), 7.39 (m, 1H), 7.20 (m, 1H), 6.30 (m, 1H), 2.22 (m, 3H), 1.72 (m, 3H), 1.25 (m, 1H), 0.99 (m, 3H). MS (EI ionization) 197 (M^+).

Example 28

Synthesis of 2-(3,6-Dihydro-2H-thiopyran-4-ylethynyl)pyridine

Reactants: 2-ethynylpyridine (6.0 mmol, 618 mg), tetrahydrothiopyran-4-one (6.0 mmol, 696 mg); yields 2-(3,6-dihydro-2*H*-thiopyran-4-ylethynyl)pyridine as a transparent oil (150 mg, 12% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.61 (m, 1H), 7.40 (m, 1H), 7.21 (m, 1H), 6.46 (m, 1H), 3.27 (m, 2H), 2.78 (m, 2H), 2.57 (m, 2H). MS (EI ionization) 201 (M^+).

Example 29

Synthesis of 2-(3,6-Dihydro-2H-pyran-4-ylethynyl)pyridine

Reactants: 2-ethynylpyridine (6.0 mmol, 618 mg), tetrahydro-4H-pyran-4-one (6.0 mmol, 600 mg); yields 2-(3,6-dihydro-2*H*-pyran-4-ylethynyl)pyridine as a transparent oil (200 mg, 18% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.63 (m, 1H), 7.44 (m, 1H), 7.21 (m, 1H), 6.29 (m, 1H), 4.25 (m, 2H), 3.81 (m, 2H), 2.36 (m, 2H). MS (EI ionization) 185 (M^+).

Example 30

Synthesis of 2-{[(1R)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-en-2-yl]ethynyl}pyridine

Reactants: 2-ethynylpyridine (6.0 mmol, 618 mg), (1*R*)-(+)-camphor (6.0 mmol, 912 mg); yields 2-{[(1*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]ethynyl}pyridine as a transparent yellow oil (125 mg, 9% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.64 (m, 1H), 7.43 (m, 1H), 7.17 (m, 1H), 6.49 (d, J= 3Hz, 1H), 2.41 (t, J= 3Hz, 1H), 1.92 (br m, 1H), 1.65 (m, 1H), 1.18 (m, 1H), 1.17 (s, 3H), 1.09 (br m, 1H), 0.84 (s, 3H), 0.82 (s, 3H). MS (EI ionization) 237 (M^+).

Example 31

Synthesis of 2-[(3,5-Dimethyl-1-cyclohexen-1-yl)ethynyl]pyridine

Reactants: 2-ethynylpyridine (6.0 mmol, 618 mg), 3,5-dimethylcyclohexanone (6.0 mmol, 0.85 mL); yields 2-[(3,5-dimethyl-1-cyclohexen-1-yl)ethynyl]pyridine as a transparent yellow oil (500 mg, 39% overall yield) as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.62 (m, 1H), 7.40 (m, 1H), 7.19 (m, 1H), 6.15 (br s, 1H), 2.29 (m, 2H), 1.80 (br m, 2H), 1.00 (m, 6H), 0.88 (br m, 2H). MS (EI ionization) 211 (M^+).

Example 32

Synthesis of 2-{[(5R)-5-Methyl-1-cyclohexen-1-yl]ethynyl}pyridine compound with 2-{[(3R)-3-methyl-1-cyclohexen-1-yl]ethynyl}pyridine (1:1)

Reactants: 2-ethynylpyridine (6.0 mmol, 618 mg), (3R)-(+)-3-methylcyclohexanone (6.0 mmol, 0.73 mL); yields 2-{[(5*R*)-5-methyl-1-cyclohexen-1-yl]ethynyl}pyridine and 2-{[(3*R*)-3-methyl-1-cyclohexen-1-yl]ethynyl}pyridine (1:1) as a transparent yellow oil (440 mg, 37% overall yield) as a mixture of regioisomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ8.56 (m, 1H), 7.62 (m, 1H), 7.40 (m, 1H), 7.18 (m, 1H), 6.31 (m, 0.5H), 6.19 (m, 0.5H), 2.30 (m, 3H), 1.85 (m, 2.5H), 1.22 (m, 1H), 0.98 (m, 3.5H). MS (EI ionization) 197 (M^+) two peaks resolved.

Example 33

Synthesis of 2-[(3E)-3-Methyl-3-penten-1-ynyl]pyridine, 2-(3-ethyl-3-buten-1-ynyl)pyridine and 2-[(3Z)-3-methyl-3-penten-1-ynyl]pyridine

Reactants: 2-ethynylpyridine (6.0 mmol, 618 mg), 2-butanone (6.0 mmol, 0.54 mL); yields 2-[(3*E*)-3-methyl-3-penten-1-ynyl]pyridine, 2-(3-ethyl-3-buten-1-ynyl)pyridine and 2-[(3*Z*)-3-methyl-3-penten-1-ynyl]pyridine as a transparent oil (135 mg, 14% overall yield) as a mixture of E, Z and exo-methylene isomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ8.59 (m, 1H), 7.65 (m, 1H), 7.44 (m, 1H), 7.20 (m, 1H), 5.88 (m, 0.75H), 5.53 (s, 0.33H) 5.40 (s, 0.33 H), 2.29 (q, J= 7Hz, 0.65H), 1.93 (m, 4.5H), 1.17 (t, J= 7Hz, 1H). MS (EI ionization) 157 (M^+) two peaks resolved.

Example 34

Synthesis of 5-Ethyl-2-(phenylethynyl)pyrimidine hydrochloride

2-Chloro-5-ethylpyrimidine (500 mg, 3.5 mmol), $PdCl_2(PPh_3)_2$ (250 mg, 0.35 mmol), CuI (203 mg, 1.06 mmol), triethylamine (6.0 mL, 43 mmol), and *n*-Bu_4NI (3.85 g, 10.4 mmol) were combined in dimethylformamide (DMF) (30 mL). The mixture was cooled in an ice bath and then phenylacetylene (1.5 mL, 14 mmol) was added. The reaction mixture was then heated to 45-50°C and after 1.5 h, additional phenylacetylene (1.5 mL, 14 mmol) was added. After an additional 17 h the reaction was diluted with ethyl acetate, washed with brine (4 x 15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting black oil was purified by column chromatography eluting with hexane then 90:10 hexane:ethyl acetate to afford 5-ethyl-2-(phenylethynyl)pyrimidine (770 mg, >100%) as a black oil. MS (EI ionization) 208 (M^+). This material was carried on to the salt formation without further purification.

5-Ethyl-2-(phenylethynyl)pyrimidine (730 mg, 3.7 mmol) was dissolved in CH_2Cl_2 (3.0 mL) and treated with HCl in diethyl ether (4.1 mL of a 1N solution, 4.1 mmol). Upon addition of the HCl solution a solid precipitated from the solution. The mixture was diluted with diethyl ether (2 mL) and

the supernatant decanted. The resultant solid was dried under high vacuum at 50°C to afford 5-ethyl-2-(phenylethynyl)pyrimidine hydrochloride (450 mg, 49 % yield) as an orange solid. M.p. 101-104°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.75 (s, 2H), 7.58-7.55 (m, 2H), 7.41-7.32 (m, 3H), 2.67 (q, J=7.6 Hz, 2H), 1.21 (t, J=7.6 Hz, 3H).

Example 35

Synthesis of 4,6-Dimethoxy-2-(phenylethynyl)pyrimidine hydrochloride

2-Chloro-4,6-dimethoxypyrimidine (500 mg, 2.9 mmol), $PdCl_2(PPh_3)_2$ (200 mg, 0.28 mmol), CuI (160 mg, 0.84 mmol), triethylamine (4.8 mL, 34 mmol), and *n*-Bu_4NI (3.2 g, 8.7 mmol) were combined in DMF (24 mL). The mixture was cooled in an ice bath and then phenylacetylene (1.25 mL, 11.4 mmol) was added. The reaction mixture was allowed to warm to ambient temperature. After 2.5 h at ambient temperature the reaction mixture was heated to 45-50°C. After 2 h, additional phenylacetylene (1.0 mL, 9.1 mmol) was added. After an additional 17 h stirring at 45-50°C, the reaction mixture was filtered through a pad of Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were washed with brine (4 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting black oil was purified by column chromatography eluting with hexane, 90:10, then 85:15 hexane:ethyl acetate to afford product contaminated with an impurity. Careful column chromatography of this impure material eluting with hexane then 90:10 hexane:ethyl acetate afforded 4,6-dimethoxy-2-(phenylethynyl)pyrimidine (320 mg, 46% yield) as a yellow solid. This material was carried on to the salt formation without further purification.

4,6-Dimethoxy-2-(phenylethynyl)pyrimidine (320 mg, 1.3 mmol) was dissolved in CH_2Cl_2 (1.0 mL), and treated with HCl in diethyl ether (1.6 mL of a 1.0M solution, 1.6 mmol). A yellow solid precipitated immediately. The mixture was diluted with ethyl acetate and allowed to stand in the freezer for 16 h. The cold supernatant was decanted and the remaining solids were triturated with ethyl acetate (1.5 mL), and then hexane (3 x 2 mL). The remaining solid was dried *in vacuo* to afford 4,6-dimethoxy-2-(phenylethynyl)pyrimidine hydrochloride (174 mg, 47 % yield) as a yellow solid. M.p. 137-138. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.65-7.62 (m, 2H), 7.46-7.42 (m, 3H), 6.16 (s, 1H), 3.97 (s, 6H).

Example 36

Synthesis of 2-[(E)-2-(3-Fluorophenyl)ethenyl]-6-methylpyrazine

2,6-Dimethylpyrazine (5.0 g, 46 mmol) was dissolved in THF (200 mL) and cooled to 0°C. Potassium *t*-butoxide (46 mL of a 1.0M solution in THF, 46 mmol) was added to afford a dark red solution. The solution was allowed to warm to ambient temperature and stir for 1 hr. The solution was then cooled to 0°C, and 3-fluorobenzaldehyde (4.9 mL, 46 mmol) was added via syringe pump over 2

h. The reaction was then allowed to slowly warm to ambient temperature. After stirring at ambient temperature for 18 h, the reaction mixture was cooled to 0°C and quenched by the addition of concentrated aqueous HCl (10 mL). The resulting suspension was allowed to warm to ambient temperature for 15 minutes, then cooled to 0°C and brought to pH=8 by addition of solid $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with 90:10, 85:15, then 80:20 hexane:ethyl acetate to afford 2-[(*E*)-2-(3-fluorophenyl)ethenyl]-6-methylpyrazine (4.14 g, 42% yield) as a light yellow solid. M.p. 43-44°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1H), 8.31 (s, 1H), 7.29 (d, J=16 Hz, 1H), 7.37-7.26 (m, 3H), 7.12 (d, J=16 Hz, 1H), 7.05-6.98 (m, 1H), 2.59 (s, 3H). MS (ESI) 214.5 (M^+). This material was carried on to the next step without further purification.

Example 37

Synthesis of 2-[1,2-Dibromo-2-(3-fluorophenyl)ethyl]-6-methylpyrazine

2-[(*E*)-2-(3-Fluorophenyl)ethenyl]-6-methylpyrazine from Example 36 (4.14 g, 19.3 mmol) was dissolved in CCl_4 (40 mL). To this solution was added a solution of bromine (1.2 mL, 23 mmol) in CCl_4 (20 mL). The brown mixture was then heated to 60°C. After 6h the suspension was treated with saturated aqueous $NaHCO_3$ (200 mL) and diluted with ethyl acetate (700 mL). The organic layer was washed with 5% aqueous $Na_2S_2O_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with 80:20 hexane:ethyl acetate then 95:5, 94:6, and 90:10 CH_2Cl_2:ethyl acetate to afford 2-[1,2-dibromo-2-(3-fluorophenyl)ethyl]-6-methylpyrazine (2.97 g, 17% over two steps) as a white solid. This material was carried on to the next step without further purification.

Example 38

Synthesis of 2-[(3-Fluorophenyl)ethynyl]-6-methylpyrazine hydrochloride

2-[1,2-Dibromo-2-(3-fluorophenyl)ethyl]-6-methylpyrazine (2.97 g, 7.94 mmol) was dissolved in THF (40 mL), treated with DBU (8.7 mL, 63 mmol), and heated to reflux. After 16 h the reaction mixture was cooled, filtered, concentrated *in vacuo*, and purified by column chromatography eluting with 80:20 then 75:25 hexane:ethyl acetate to afford 2-[(3-fluorophenyl)ethynyl]-6-methylpyrazine (427 mg, 25% yield). This material was carried on to the salt formation without further purification.

2-[(3-Fluorophenyl)ethynyl]-6-methylpyrazine (520 mg, 2.45 mmol) was dissolved in CH_2Cl_2 (3 mL), and the resulting solution was treated with HCl in diethyl ether (2.7 mL of a 1.0M solution, 2.7 mmol). The mixture was sonicated, and the solvent decanted. The remaining solid was dried under high vacuum to afford 2-[(3-fluorophenyl)ethynyl]-6-methylpyrazine hydrochloride (338 mg, 60%

yield) as a light yellow solid. M.p. 62-63°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.57 (s, 1H), 7.54-7.35 (m, 3H), 7.28-7.20 (m, 3H), 2.84 (s, 3H).

Example 39

Synthesis of 1-Chloro-4-(1-cyclohexen-1-yl)-3-butyn-2-one

Anhydrous $ZnCl_2$ (5.0 g, 37 mmol) was dissolved in THF (25 mL) and the solution cooled to 0°C in an ice bath. In another flask 1-ethynylcyclohexene (4.3 mL, 36.3 mmol) was dissolved in THF (25 mL), cooled to 0°C in an ice bath, and treated with *n*-butyllithium (15.7 mL of a 2.2M solution in hexane, 34.5 mmol). After 20 minutes the cyclohexenylethynyllithium solution was added via cannula to the $ZnCl_2$ solution. After an additional 20 minutes $Pd(PPh_3)_4$ (620 mg, 0.54 mmol) was added to the alkynylzinc solution. The resulting yellow solution was treated with chloroacetyl chloride (4.2 mL, 55 mmol) dropwise over 10 minutes. After 2 h at 0°C the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (500 mL), and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3 x 200 ml) and the combined organic layers were washed with water (200 ml), brine (200 ml), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford a dark brown oil that was purified by column chromatography eluting with hexane, then 99:1 hexane:ethyl acetate to afford 1-chloro-4-(1-cyclohexen-1-yl)-3-butyn-2-one (4.4 g, 67% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.56 (m, 1H), 4.23 (s, 2H), 2.19 (m, 4H), 1.68-1.62 (m, 4H). MS (EI ionization) 182 (^{35}Cl M^+), 184 (^{37}Cl M^+). The material was carried on to the next step without further purification.

Example 40

Synthesis of 4-(1-Cyclohexen-1-ylethynyl)-2-methyl-1,3-thiazole, p-toluenesulfonic acid salt

1-Chloro-4-(1-cyclohexen-1-yl)-3-butyn-2-one (2.0 g, 11.0 mmol) was dissolved in DMF (10.0 mL), thioacetamide (950 mg, 12.6 mmol) was added, and the resulting pale brown solution was stirred at ambient temperature for 64 h. The reaction mixture was diluted with ethyl acetate (300 mL), washed with saturated $NaHCO_3$ solution (300 mL), water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, adsorbed onto silica gel and purified by column chromatography eluting with hexane, 99:1 then 98:2 hexane:ethyl acetate to afford 4-(1-cyclohexen-1-ylethynyl)-2-methyl-1,3-thiazole (620 mg, 28% yield) as a yellow powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (s, 1H), 6.27-6.24 (m, 1H), .2.7 (s, 3H) 2.22-2.12 (m, 4H), 1.68-1.58 (m, 4H).

4-(1-Cyclohexen-1-ylethynyl)-2-methyl-1,3-thiazole (620 mg, 3.1 mmol) was dissolved in ethanol (30 mL) at ambient temperature. *p*-Toluenesulfonic acid monohydrate (580 mg, 3.1 mmol) was

added in one portion to afford a brown solution. After all of the acid had dissolved the reaction mixture was stirred for several minutes and then concentrated *in vacuo* to afford a dark brown oil which solidified under high vacuum. The crude material was dissolved in hot ethyl acetate. After cooling to ambient temperature the material was stored in the freezer for few hours. The supernatant solution was decanted and the crystalline solids were dried under high vacuum to afford crystalline 4-(1-cyclohexen-1-ylethynyl)-2-methyl-1,3-thiazole p-toluenesulfonate salt (882 mg , 74% yield) as yellow crystals. M.p. 128-129°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.87 (s, 1H), 7.71-7.68 (d, J=9 Hz, 2H), 7.24-7.21 (d, J=9Hz, 3H), 6.38 (m,.1H), 2.88, (s, 3H), 2.36 (s, 3H), 2.21-2.17 (m, 4H), 1.68-1.64 (m, 4H).

Example 41

Synthesis of 4-(1-Cyclohexen-1-ylethynyl)-1,3-thiazol-2-ylamine, p-toluenesulfonic acid salt

1-Chloro-4-(1-cyclohexen-1-yl)-3-butyn-2-one (2.0 g, 11 mmol) was dissolved in DMF (10.0 mL), thiourea (996 mg, 13.1 mmol) was added, and the resulting pale brown solution was stirred at ambient temperature for 16 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with saturated $NaHCO_3$ solution (100 mL), water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The dark oil was dissolved in ethyl acetate, adsorbed onto silica gel and purified by column chromatography eluting with 9:1 then 3:1 hexane:ethyl acetate to afford 4-(1-cyclohexen-1-ylethynyl)-1,3-thiazol-2-ylamine (1.1 g, 49% yield) as an off-white solid. MS (EI ionization) 204 (M+).

4-(1-Cyclohexen-1-ylethynyl)-1,3-thiazol-2-ylamine (1.1g, 5.4 mmol) was dissolved in ethanol (40 mL) at ambient temperature. *p*-Toluenesulfonic acid monohydrate (1.0 g, 5.4 mmol) was added in one portion to afford a brown solution. After all of the acid had dissolved the reaction mixture was stirred for several minutes and then concentrated *in vacuo* to afford a dark brown oil which solidified under high vacuum. The crude material was dissolved in hot ethyl acetate. After cooling to ambient temperature the material was stored in the freezer. After several hours in the freezer, the supernatant solution was decanted and the crystalline solids were dried under high vacuum to afford 4-(1-cyclohexen-1-ylethynyl)-1,3-thiazol-2-ylamine p-toluenesulfonate salt (1.84 g, 87% yield) as off-white powder. M.p. 188-189°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.72 –7.69 (d, J=9 Hz, 2H), 7.24-7.22 (d, J=6 Hz, 2H), 6.94 (s, 1H), 6.34-6.32 (m, 1H), 2.36 (s, 3H), 2.19-2.15 (m, 4H) 1.70-1.61 (m, 4H).

Example 42

Synthesis of 2-(1-Cyclohexen-1-ylethynyl)-6-methylpyridine

2-Bromo-6-methyl pyridine (2.0 g, 12 mmol) and CuI (440 mg, 2.3 mmol) were combined in DME (30 mL), and argon gas was bubbled through the suspension for several minutes to deoxygenate

the mixture. Triethylamine (8.0 mL, 58 mmol) and $PdCl_2(PPh_3)_2$ (814 mg, 1.16 mmol) were added, followed by the dropwise addition of 1-ethynylcyclohexene (1.7 g, 15 mmol). The reaction was stirred at ambient temperature overnight. GC/MS showed no starting 2-bromo-6-methylpyridine remaining. The mixture was diluted with ethyl acetate (100 mL), and filtered through Celite™. The pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with hexane then 99:1, 98:2 hexane:ethyl acetate to afford 2-(1-cyclohexen-1-ylethynyl)-6-methylpyridine (1.8 g, 79% yield) as a red oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.46 (m, 1H), 7.21 (d, J=9 Hz, 1H), 7.03 (d, J=9 1H), 6.32-6.29 (m, 1H), 2.53 (s, 3H), 2.24-2.21 (m, 2H), 2.14-2.12 (m, 2H), 1.67-1.57 (m, 4H). MS (ESI) 198.1 (M^+).

Example 43

Synthesis of 2-(Cyclohexylethynyl)-6-methylpyridine

2-Bromo-6-methyl pyridine (2.0 g, 11.6 mmol) and CuI (440 mg, 2.3 mmol) were combined in DME (30 mL), and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8.0 mL, 58 mmol) and $PdCl_2(PPh_3)_2$ (814 mg, 1.16 mmol) were added, followed by the dropwise addition of cyclohexylethyne (1.25 g, 11.6 mmol). The reaction was stirred at ambient temperature overnight. GC/MS showed no starting 2-bromo-6-methylpyridine remaining. The mixture was diluted with ethyl acetate (100 mL), and filtered through Celite™. The pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with hexane then 98:2, 96:4 hexane:ethyl acetate to afford 2-(cyclohexylethynyl)-6-methylpyridine (1.78 g, 77% yield) as a pale brown liquid that partially solidified on standing in the freezer. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52-7.46 (m, 1H), 7.20 (d, J=9 Hz, 1H), 7.03 (d, J=9 Hz, 1H), 2.6 (m,1 H), 2.54 (s, 3H), 2.93-2.89 (m, 2H), 1.78-1.73 (m, 2H), 1.57-1.54 (m, 3H), 1.36-1.32 (m, 3H). MS (ESI) 200.1 (M^++H).

Example 44

Preparation of 4-Methyl-2-[(E)-2-phenylethenyl]-1,3-oxazole

Cinnamamide (2.0 g, 14 mmol), chloroacetone (0.93 mL, 16 mmol), and K_2CO_3 (940 mg, 6.8 mmol) were combined under argon and the mixture was heated in a 120° C oil bath. The reaction mixture solidified and stirring stopped upon heating. After 16 h, the cooled reaction mixture was quenched by the addition of water (20 mL) and then diluted with ethyl acetate (100 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with 90:10 hexane:ethyl acetate. The product that was obtained (280 mg) showed some close running impurities by thin layer chromatography (TLC). The material was

further purified by preparative TLC via multiple elutions with 95:5 hexane:ethyl acetate. Isolation of the middle of the main band afforded 4-methyl-2-[(*E*)-2-phenylethenyl]-1,3-oxazole (47.0 mg, 2% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53-7.32 (m, 7H), 6.91 (d, J=16.4 Hz, 1H), 2.21 (s, 3H). MS (ESI) 185.7 (M^++H).

Example 45

4-Methyl-2-[2-phenylethenyl]-1,3-thiazole

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of Ethyl 4-methyl-1,3-thiazole-2-carboxylate: Ethyl thiooxamate (3.0 g, 22 mmol) was dissolved in ethanol (30 mL) under argon. Chloroacetone (1.8 mL, 22 mmol) was added and the resultant solution was heated at 80° C for 16 h. The reaction mixture was concentrated *in vacuo*, adsorbed onto silica gel, and purified by column chromatography on silica gel eluting with 97:3, then 95:5 hexane:ethyl acetate to afford ethyl 4-methyl-1,3-thiazole-2-carboxylate (850 mg, 22% yield) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.20 (s, 1H), 4.48 (q, J=7.1 Hz), 2.56 (s, 3H), 1.47 (s, 3H). MS (EI ionization) 171 (M^+).

Preparation of (4-Methyl-1,3-thiazol-2-yl)methanol: Ethyl 4-methyl-1,3-thiazole-2-carboxylate (450 mg, 2.6 mmol) was dissolved under argon in tetrahydrofuran (THF) (5 mL). The solution was cooled to 0° C in an ice bath and treated with diisobutylaluminum hydride (5.3 mL of a 1.5M solution in toluene, 7.9 mmol). The reaction mixture was allowed to slowly warm to ambient temperature over 16 h and then cooled to -78° C and cautiously quenched by the dropwise addition of methanol. After gas evolution had ceased, saturated aqueous sodium-potassium tartrate (10 mL) was added, and the reaction mixture was allowed to warm to ambient temperature. The aqueous phase was extracted with ethyl acetate (3 x 30 mL), the combined organics dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 90:10 then 1:1 hexane:ethyl acetate to afford (4-methyl-1,3-thiazol-2-yl)methanol (180 mg, 53% yield) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.81 (s, 1H), 4.84 (s, 3H), 2.36 (s, 3H). MS (EI ionization) 129 (M^+).

Preparation of 4-Methyl-1,3-thiazole-2-carbaldehyde: (4-Methyl-1,3-thiazol-2-yl)methanol (180 mg, 1.4 mmol) was dissolved in CH_2Cl_2 (9 mL), and treated with Magtrieve™ (2.5 g). The resultant suspension was heated to reflux for 16 h. The reaction mixture was cooled and filtered through a pad of Celite™. The filter pad was washed thoroughly with CH_2Cl_2 and the combined filtrates were concentrated *in vacuo* to afford 4-methyl-1,3-thiazole-2-carbaldehyde (120 mg, 67% yield) as an oil. The material was carried on to the next step without further purification. MS (EI ionization) 127 (M^+).

Preparation of 4-Methyl-2-[2-phenylethenyl]-1,3-thiazole: Sodium hydride (102 mg of a 60% suspension in mineral oil, 4.3 mmol) was slurried in dry 1,2-dimethoxyethane (DME) under argon, cooled to 0° C in an ice bath, and diethylbenzyl phosphonate (0.89 mL, 4.3 mmol) was added dropwise to the suspension. Thirty minutes after the completion of the phosphonate addition, 4-methylthiazole-2-carboxaldehyde (120 mg, 0.94 mmol) was added as a solution in DME (5 mL). After stirring for 4 h, further NaH (40 mg of a 60% suspension in mineral oil, 1.0 mmol) was added and the reaction mixture was allowed to warm to ambient temperature and stir for 16 h. The reaction mixture was quenched by the addition of water (20 mL) and ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (2 x 30 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 90:10 hexane:ethyl acetate to afford 4-methyl-2-[2-phenylethenyl]-1,3-thiazole (30 mg, 16% yield) as an oil. ^1H NMR analysis showed the material to be a 10:1 mixture of E and Z isomers (spectral data are reported for the major isomer). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.54-7.51 (m, 2H) 7.42-7.23 (m, 5H) 6.80 (s, 1H) 2.47 (s, 3H). MS (ESI) (minor isomer) 202.2 (M^++H), (major isomer) 201.6 (M^+).

Example 46

2-Methyl-4-[(E)-2-phenylethenyl]-1,3-thiazole

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of Ethyl 2-methyl-1,3-thiazole-4-carboxylate: Thioacetamide (7.6 g, 100 mmol) was added to ethanol (60 mL), and the resultant suspension was cooled to 0° C and treated with ethyl bromopyruvate (12.5 mL, 100 mmol). The resultant solution was stirred for five minutes at 0° C at which time the ice bath was removed and the solution was allowed to warm to ambient temperature. After 0.5 h at ambient temperature, the solution was heated to reflux. After 12 h, the solvents were removed *in vacuo*, and the resultant crude product was taken up in ethyl acetate (300 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL), and the basic aqueous solution was then extracted with additionalethyl acetate (2 x 50 mL). The combined organic solutions were washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford a yellow waxy solid. The crude product was dissolved in a small amount of hot ethyl acetate, diluted with hot hexane, and the resultant solution was allowed to cool to ambient temperature, seeded with a small amount of crude product, and transferred to the freezer. After 16 h the crystalline product was collected, washed with cold 8:1 hexane:ethyl acetate, and allowed to dry under high vacuum to afford ethyl 2-methyl-1,3-thiazole-4-carboxylate (11.76 g, 69% yield) as large brownish crystals. M.p. 56-58.5°C. 1H NMR (CDCl3, 300 MHz) δ 8.06 (s, 1H), 4.43 (q, 2H), 2.78 (s, 3H), 1.42 (t, 3H). MS (EI ionization) 171 (M+).

Preparation of (2-Methyl-1,3-thiazol-4-yl)methanol: Ethyl 2-methyl-1,3-thiazole-4-carboxylate (15 g, 60 mmol) was slurried in THF (40 mL) and cooled to 0°C. Lithium aluminum hydride (60 mL of a 1M solution in THF) was added slowly and the reaction mixture was allowed to warm to 25° C. After 16 h the reaction was quenched by the dropwise addition of water (2.28 mL), 15% NaOH solution (2.28 mL) and then water (6.84 mL). Ethyl acetate (100 mL) was added, the reaction mixture filtered, and the filtrate concentrated *in vacuo*. The crude residue was chromatographed on silica gel with ethyl acetate:hexane (1:1) as eluant to afford (2-methyl-1,3-thiazol-4-yl)methanol as an oil (4.41 g, 57%). This material was carried on to the next step without further purification.

Preparation of 2-Methyl-1,3-thiazole-4-carbaldehyde: (2-Methyl-1,3-thiazol-4-yl)methanol (4.4 g , 34 mmol) was dissolved in CH_2Cl_2 (400 mL). Magtrieve™ (44 g) was added and the reaction was heated under reflux for 24 h. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford 2-methyl-1,3-thiazole-4-carbaldehyde (3.7g, 86% yield) as a yellow oil which was carried on to the next step without further purification. 1H NMR (CDCl3, 300 MHz) δ 9.98 (s, 1H), 8.06 (s, 1H,), 2.79 (s, 3H,). MS (EI ionization) 127 (M+).

Preparation of 2-Methyl-4-[(E)-2-phenylethenyl]-1,3-thiazole: Sodium hydride (120 mg of a 60% suspension in mineral oil, 3.0 mmol) was slurried in DME (6 mL) and cooled to 0° C. Diethyl benzylphosphonate (1.1 g, 5.0 mmol) was added dropwise and after 15 minutes, 2-methyl-1,3-thiazole-4-carbaldehyde (320 mg, 2.5 mmol) in DME (5 mL) was added dropwise to the reaction mixture. After 3 h at 0° C the reaction mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous NH_4Cl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 90:10 hexane:ethyl acetate to afford 2-methyl-4-[(E)-2-phenylethenyl]-1,3-thiazole (330 mg, 65% yield) as an oil. 1H NMR (CDCl3, 300 MHz) δ 7-7.5 (m, 8H), 2.7 (s, 3H). MS (ESI) 202.1 (M++H).

Example 47

2-Methyl-4-(phenylethynyl)-1,3-thiazole, p-toluenesulfonic acid salt

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of 1-Chloro-4-phenyl-3-butyn-2-one: Anhydrous $ZnCl_2$ (10 g, 73 mmol) was dissolved in THF (50 mL) and the solution cooled to 0° C in an ice bath. In another flask phenylacetylene (8.0 mL, 73 mmol) was dissolved in THF (50 mL), cooled to 0° C in an ice bath, and

treated with n-butyllithium (32 mL of a 2.2M solution in hexane, 70 mmol). After 20 minutes the phenylethynyllithium solution was added via cannula to the $ZnCl_2$ solution. After an additional 20 minutes $Pd(PPh_3)_4$ (1.23 g, 1.06 mmol) was added to the alkynylzinc solution. The resulting yellow solution was treated with chloroacetyl chloride (8.8 mL, 110 mmol) dropwise over 10 minutes. After 2 h at 0° C the reaction mixture was quenched by the addition of cold aqueous 1M HCl (50 mL), and diethyl ether (500 mL). The acidic aqueous was extracted with diethyl ether (2 x 50 mL) and the combined organic extracts were washed with water (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The dark solution was dried and decolorized over Na_2SO_4, and charcoal and filtered through a pad of Celite™. The pad was washed thoroughly with ethyl acetate and the combined filtrates were concentrated *in vacuo* to afford a dark brown oil. The crude product was purified by column chromatography eluting with hexane, 99:1, 98:2, 96:4, then 94:6 hexane:ethyl acetate to afford 1-chloro-4-phenyl-3-butyn-2-one (7.83 g, 60% yield) as an orange oil which darkened and partially solidified upon standing in the freezer. 1H NMR (CDCl3, 300 MHz) δ 7.63-7.60 (m, 2H), 7.53-7.39 (m, 3H), 4.33 (s, 3H). MS (EI ionization) 178 (35Cl M+), 180 (37Cl M+).

Preparation of 2-Methyl-4-(phenylethynyl)-1,3-thiazole, p-toluenesulfonic acid salt: 1-Chloro-4-phenyl-3-butyn-2-one (1.6 g, 9.1 mmol) was dissolved in dry acetonitrile (15 mL), treated with thioacetamide (680 mg, 9.1 mmol), and heated to reflux for 4 h. After cooling, the acetonitrile was removed *in vacuo*, and the residue was partitioned between water (50 mL) and ethyl acetate (150 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated *in vacuo*, adsorbed onto silica gel, and purified by column chromatography on silica gel eluting with 99:1, 98:2, then 95:5 hexane:ethyl acetate to afford 2-methyl-4-(phenylethynyl)-1,3-thiazole (240 mg, 13% yield) as a red oil. 1H NMR (CDCl3, 300 MHz) δ 7.58-7.54 (m, 2H), 7.40-7.34 (m, 4H), 2.74 (s, 3H). MS (EI ionization) 199 (M+).

2-Methyl-4-(phenylethynyl)-1,3-thiazole (270 mg, 1.35 mmol) was dissolved in ethanol (6 mL) at ambient temperature. p-Toluenesulfonic acid monohydrate (252 mg, 1.32 mmol) was added in one portion to afford a brown solution. After all of the acid had dissolved the reaction mixture was stirred for several minutes and then concentrated *in vacuo* to afford a dark brown oil which partially solidified under high vacuum. The crude material was triturated with diethyl ether, and the resulting solids were taken up in hot ethyl acetate. The hot solution was treated with decolorizing carbon and filtered hot to afford a pale brown solution, which was treated with hexane until cloudy, then heated to afford a clear solution. The solution was seeded with authentic product and allowed to crystallize. After cooling to ambient temperature the material was stored in the freezer for 16 h. The supernatant solution was decanted and the crystalline solids were pumped down under high vacuum to afford crystalline 2-methyl-4-(phenylethynyl)-1,3-thiazole, p-toluenesulfonic acid salt (260 mg, 52% yield) as brown crystals. M.p. 131-132.5°C. 1H NMR (CD3OD, 300 MHz) δ 7.99 (s, 1H), 7.70 (d, J=8.1Hz), 7.60-7.57 (m, 2H), 7.46-7.43 (m, 3H), 7.23 (d, J=8 Hz, 2H), 2.89, (s, 3H), 2.36 (s, 3H). MS (ESI) 199.7 (M++H).

Example 48

Preparation of 4-(Phenylethynyl)-1,3-thiazol-2-amine, p-toluenesulfonic acid salt

1-Chloro-4-phenyl-3-butyn-2-one (245 mg, 1.37 mmol) was dissolved in DMF (1.0 mL), thiourea (126 mg, 1.66 mmol) was added, and the resulting pale brown solution was stirred at ambient temperature for 5 days. The reaction mixture was diluted with Ethyl acetate (50 mL), washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The dark oil was dissolved in methanol, adsorbed onto silica gel and purified by column chromatography eluting with 4:1, 3:1, then 2:1 hexane:ethyl acetate to afford 4-(phenylethynyl)-1,3-thiazol-2-amine (56 mg, 20% yield) as an oil. 1H NMR (CDCl3, 300 MHz) δ 7.53-7.50 (m, 2H), 7.37-7.32 (m, 3H), 6.77 (s, 1H), 5.41 (br s, 2H). MS (EI ionization) 200 (M+).

4-(Phenylethynyl)-1,3-thiazol-2-amine (700 mg, 3.5 mmol) was dissolved in ethanol (20 mL) at ambient temperature. p-Toluenesulfonic acid monohydrate (660 mg, 3.5 mmol) was added in one portion to afford a brown solution. After all of the acid had dissolved the reaction mixture was stirred for several minutes and then concentrated *in vacuo* to afford a dark brown oil which solidified under high vacuum. The crude material was dissolved in hot ethyl acetate containing a few drops of methanol. After cooling to ambient temperature the material was stored in the freezer for few hours. The supernatant solution was decanted and the crystalline solids were dried under high vacuum to afford crystalline 4-(phenylethynyl)-1,3-thiazol-2-amine, p-toluenesulfonic acid salt (1.0 g , 73% yield) as brown crystals. M.p. 131-132.5°C. 1H NMR (CD3OD, 300 MHz) δ 7.73 –7.70 (d, J=9 Hz, 2H), 7.56-7.52 (dd, J=9, 2 Hz, 2H), 7.48-7.37 (m, 3H), 7.23-7.20 (d, J=9Hz, 2H), 7.12, (s, 1H), 2.34 (s, 3H).

Example 49

4-Methyl-5-(phenylethynyl)-1,3-thiazole

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of 5-Bromo-4-methyl-1,3-thiazole: N-Bromosuccinimide (30 g, 170 mmol) was suspended in CCl_4 (150 mL) and 4-methylthiazole (15 g, 150 mmol) was added in one portion. The mixture was heated under reflux for 4 h then allowed to cool to ambient temperature. The reaction mixture was diluted with ethyl acetate (500 mL) and washed with water, then brine. The organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 9:1 hexane:methylene chloride to afford 5-bromo-4-methyl-1,3-thiazole (6.8g, 24% yield) as a dark reddish oil. 1H NMR (CDCl3, 300 MHz) δ 8.69 (s, 1H), 2.44 (s, 3H). MS (EI ionization) 177 (35Cl M+), 179 (37Cl M+).

Preparation of 4-Methyl-5-(phenylethynyl)-1,3-thiazole: 5-Bromo-4-methyl-1,3-thiazole (570mg, 3.2 mmol) and CuI (120 mg, 0.63 mmol) were combined in DME (5 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (2.0 mL, 14 mmol) and $PdCl_2(PPh_3)_2$ (220 mg, 0.32 mmol) were added, followed by the dropwise addition of phenylacetylene (1.0 mL, 9.5 mmol). After 16 h stirring at ambient temperature additional phenylacetylene (0.35 mL, 3.2 mmol), CuI, (61 mg, 0.32 mmol), and $PdCl_2(PPh_3)_2$ (110 mg, 0.16 mmol) were added and the reaction mixture was stirred for a further 16 h. The reaction was then heated to reflux, and after 3 h the reaction mixture was cooled, diluted with ethyl acetate (20 mL), and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate and the combined filtrates were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 95:5 hexane:ethyl acetate to afford 4-methyl-5-(phenylethynyl)-1,3-thiazole (166 mg, 26% yield) as a red oil. 1H NMR (CDCl3, 300 MHz) δ 8.62 (s, 1H), 7.54-7.50 (m, 2H), 7.37-7.26 (m, 3H), 2.6 (s, 3H). MS (ESI) 200.1 (M++H).

Example 50

5-[(2-Fluorophenyl)ethynyl]-4-methyl-1,3-thiazole

5-Bromo-4-methyl-1,3-thiazole (500 mg, 2.8 mmol) and CuI (120 mg, 0.63 mmol) were combined in DME (5 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (2.0 mL, 14 mmol) and $PdCl_2(PPh_3)_2$ (220 mg, 0.32 mmol) were added, followed by the dropwise addition of (2-fluorophenyl)acetylene (1.0 g, 8.3 mmol) . The reaction mixture was heated and after 3 h at reflux, allowed to cool, diluted with ethyl acetate (20 mL), and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate and the combined filtrates were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with 95:5 hexane:ethyl acetate to afford 5-[(2-fluorophenyl)ethynyl]-4-methyl-1,3-thiazole (690 mg, 56% yield) as a red oil. 1H NMR (CDCl3, 300 MHz) δ 8.65 (s, 1H), 7.53-7.47 (m, 1H), 7.36-7.26 (m, 1H), 7.17-7.09 (m, 2H), 2.62 (s, 3H). MS (ESI) 217.3 (M+).

Example 51

2-(Phenylethynyl)-1,3-thiazole, p-toluenesulfonic acid salt

2-Bromo-1,3-thiazole (2.0 g, 12 mmol) and CuI (460 mg, 2.4 mmol) were combined in DME (40 mL), and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8.6 mL, 62 mmol) and PdCl2(PPh3)2 (856 mg, 1.22 mmol) were added and then phenylacetylene (3.7g, 36.5 mmol) was added dropwise. The reaction was heated to reflux at which point the reaction mixture solidified. Additional DME (20 mL) was added to dissolve the solids and the reaction mixture was allowed to stir for 16 h at reflux, at which time GC/MS showed no

remaining 2-bromothiazole. After cooling, the mixture was diluted with 200 mL ethyl acetate, and filtered through Celite™. The pad was then washed thoroughly with ethyl acetate and the combined filtrates were washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with hexane, then 97:3 hexane:ethyl acetate) to afford 2-(phenylethynyl)-1,3-thiazole (1.3 g, 60% yield) as a yellowish oil. 1H NMR (CDCl3, 300 MHz) δ 7.86 (d, J=3.2 Hz, 1H), 7.61-7.57 (m, 2H), 7.42-7.26 (m, 4H). MS (ESI) 185.2 (M+).

2-(Phenylethynyl)-1,3-thiazole (3.00 g, 16.2 mmol) was dissolved in ethanol (75 mL) at ambient temperature. p-Toluenesulfonic acid monohydrate (3.08 g, 16.2 mmol) was added in one portion to afford a yellow solution. After all of the acid had dissolved the reaction mixture was stirred for several minutes and then concentrated *in vacuo* to afford a bright yellow solid. An attempt was made to recrystallize the material from hot ethyl acetate:hexane, but the recovery of solid after cooling was poor. Analysis of the crude material from the reaction showed it to be of sufficient purity. 2-(Phenylethynyl)-1,3-thiazole, p-toluenesulfonic acid salt (4.77 g, 82% yield) was obtained as a bright yellow powder that turns beige upon standing at ambient temperature. M.p. 130-132°C. 1H NMR (CD3OD, 300 MHz) δ 8.17 (d, J=3.7 Hz, 1H), 8.05 (d, J=3.7 Hz, 1H), 7.72-7.67 (m, 4 H), 7.56-7.46 (m, 3 H), 7.22 (d, J=8 Hz, 2 H), 2.35 (s, 3 H). MS (ESI) 186.1 (M++H).

Example 52

4-Bromo-2-(phenylethynyl)-1,3-thiazole

2,4-Dibromo-1,3-thiazole (2.0 g, 8.2 mmol) and CuI (312 mg, 1.64 mmol) were combined in DME (25 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (5.7 mL, 41 mmol) and $PdCl_2(PPh_3)_2$ (580 mg, 0.82 mmol) were added, and then phenylacetylene (0.90 mL, 8.6 mmol) was added dropwise. The reaction was stirred for 4 h at ambient temperature at which point GC/MS analysis showed the reaction to be complete . The mixture was filtered through Celite™, the filter pad was washed thoroughly with Ethyl acetate and the combined filtrates were then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, then 97:3 hexane:ethyl acetate to afford pure 4-bromo-2-(phenylethynyl)-1,3-thiazole (1.0 g, 46% yield) as a colorless solid. M.p. 79-82°C; 1H NMR (CDCl3, 300 MHz) δ 7.60-7.56 (m, 2H) 7.45-7.26 (m, 3H), 7.26 (s, 1H). MS (EI ionization) 263 (M+, 79Br), 265 (M+, 81Br).

Example 53

5-Methyl-2-(phenylethynyl)-1,3-thiazole

4-Bromo-2-(phenylethynyl)-1,3-thiazole (500 mg, 1.89 mmol) was dissolved in dry THF (10 mL) under argon, cooled to -78°C, then t-butyllithium (1.7 mL of a 1.7M solution in pentane, 2.8 mmol) was added. After 30 min 0.4 mL of the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. GC/MS of the crude product from this workup and comparison with a GC/MS of authentic 2-(2-phenylethynyl)-thiazole showed the two to be identical. This confirmed that the initial coupling with phenylacetylene (in Example 9) took place at the bromine at the 2 position rather than at the 4 position. The GC/MS also showed that the reaction was not complete. Additional t-butyllithium (1.7 mL of a 1.7M solution in pentane, 2.8 mmol) was added. After 30 minutes iodomethane (0.36 mL, 5.7 mmol) was added to the reaction mixture, and the reaction was allowed to warm to ambient temperature for 16 h. The solvents were then removed *in vacuo*, and residue dissolved in ethyl acetate (50 mL), washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with hexane, 99:1, 98:2, 97.5:2.5 hexane:ethyl acetate to afford 2-(2-phenylethynyl)-5-methyl-1,3-thiazole (90 mg). 1H NMR analysis of the material showed it to be impure, despite its apparent homogeneity by TLC analysis. The crude compound was dissolved in DMSO and purified by preparative HPLC with a 30 min gradient from 70:30 water:acetonitrile to 100% acetonitrile to afford pure 5-methyl-2-(phenylethynyl)-1,3-thiazole as a white powder (44 mg, 24% yield). M.p. 82-83°C. 1H NMR (CDCl3, 300 MHz) δ 7.85-7.55 (m, 2H), 7.49 (d, J=0.6 Hz, 1H), 7.37-7.32 (m, 3H), 2.49 (s, 3H). MS (ESI) 200.1 (M++H).

Example 54

2-[(3-Methylphenyl)ethynyl]-1,3-thiazole

2-Bromo-1,3-thiazole (2.0 g, 13 mmol) and CuI (330 mg, 1.7 mmol) were combined in DME (25 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (5.7 mL, 43 mmol) and $PdCl_2(PPh_3)_2$ (604 mg, 0.86 mmol) were added and m-tolylacetylene (1.0 g, 8.6 mmol) was added dropwise. The reaction mixture was heated under reflux for 4 h at which time GC/MS showed the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 98:2 hexane:ethyl acetate to afford 2-[2-(3-methylphenyl)ethynyl]-thiazole (280 mg, 16% yield) as a yellow oil which was still impure by 1H NMR analysis. The compound (280 mg) was dissolved in DMSO and purified by preparative HPLC with a 30 min gradient from 70:30 water:acetonitrile to 100% acetonitrile to afford pure 2-[(3-

methylphenyl)ethynyl]-1,3-thiazole (122 mg, 6% yield) as a yellow oil. 1H NMR (CDCl3, 300 MHz) δ 7.84 (d, J=3.0 Hz, 1H), 7.40-7.34 (m, 3H), 7.28-7.18 (m, 2H), 2.34 (s, 3H). MS (ESI) 200.1 (M++H).

Example 55

2-[(4-Fluorophenyl)ethynyl]-1,3-thiazole

2-Bromo-1,3-thiazole (1.0 g, 6.2 mmol) and CuI (152.4 mg, 0.8 mmol) were combined in DME (17 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (3 mL, 21 mmol) and $PdCl_2(PPh_3)_2$ (280 mg, 0.40 mmol) were added and 1-ethynyl-4-fluorobenzene (500 mg, 4.2 mmol) was added dropwise. The reaction was heated under reflux for 4 h at which time GC/MS showed the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with Ethyl acetate. The combined filtrates were then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 98:2 hexane:ethyl acetate to 2-[(4-fluorophenyl)ethynyl]-1,3-thiazole as a white solid which was impure by ^{1}H NMR analysis. The compound (280 mg) was dissolved in DMSO and purified by preparative HPLC with a 30 min gradient from 60:40 water:acetonitrile to 100% acetonitrile to afford 2-[(4-fluorophenyl)ethynyl]-1,3-thiazole (33 mg, 3% yield) as a white solid. M.p. 78-79°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J=3.0 Hz, 1H), 7.60-7.55(m, 2H), 7.39 (d, J=3.0 Hz, 1H), 7.14-7.00 (m, 2H). MS (ESI) 204 (M^++H).

Example 56

2-[(2-Fluorophenyl)ethynyl]-1,3-thiazole

2-Bromo-1,3-thiazole (2.0 g, 13 mmol) and CuI (316 mg, 1.6 mmol) were combined in DME (25 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (5.8 mL, 42 mmol) and $PdCl_2(PPh_3)_2$ (580 mg, 0.83 mmol) were added and 1-ethynyl-2-fluorobenzene (1.0 g, 8.3 mmol) was added dropwise. The reaction was heated under reflux for 4 h at which time GC/MS showed the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL) and washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 98:2 hexane:ethyl acetate to afford 2-[(2-fluorophenyl)ethynyl]-1,3-thiazole (700 mg, 41% yield) as a yellow oil that was impure by ^{1}H NMR analysis. The compound (140 mg) was dissolved in DMSO and purified by preparative HPLC with a 30 min gradient from 50:50 water:acetonitrile to 100% acetonitrile to afford 2-[(2-fluorophenyl)ethynyl]-1,3-thiazole (53.2 mg, 75% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, J=3.0 Hz, 1H), 7.59-7.53 (m, 1H), 7.42-7.35 (m, 2H), 7.18-7.09 (m, 2H). MS (ESI) 204 (M^++H).

Example 57

4,5-Dimethyl-2-(phenylethynyl)-1,3-thiazole.

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of 2-Bromo-4,5-dimethyl-1,3-thiazole: 4,5-Dimethyl-1,3-thiazole (5.0 g, 44 mmol) was dissolved in carbon tetrachloride (60 mL), and *N*-bromosuccinimide (8.19 g, 46 mmol) was added. The resulting mixture was heated to reflux while protected from light with aluminum foil. After ½ h at reflux the dark suspension was cooled and allowed to stand at ambient temperature for 16 h. The reaction mixture was then heated to reflux for an additional 4 h and cooled to ambient temperature. After standing at ambient temperature for 16 h, GC/MS analysis showed mostly monobromide, with a small amount of starting 4,5-dimethyl-1,3-thiazole present. The yellow supernatant solution was decanted from the black solids that had deposited on the walls of the flask. The crude product was concentrated *in vacuo*, and then further purified by column chromatography eluting with hexane, 99:1, 98:2, 96:4, 94:6, then 90:10 hexane:ethyl acetate to afford 2-bromo-4,5-dimethyl-1,3-thiazole (1.34 g, 16 % yield) as a white semi-solid. M.p. 55-60°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H), 2.30 (s, 3H). MS (EI ionization) 191 (M^+, ^{79}Br), 193 (M^+, ^{81}Br).

Preparation 4,5-Dimethyl-2-(phenylethynyl)-1,3-thiazole: 2-Bromo-4,5-dimethyl-1,3-thiazole (1.3 g, 6.8 mmol) and CuI (190 mg, 1.36 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (5.0 mL, 34 mmol) and PdCl2(PPh3)2 (477 mg, 0.68 mmol) were added and phenylacetylene (1.86 g, 18.9 mmol) was added dropwise. After stirring at ambient temperature for 16 h, GC/MS showed the reaction was complete. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with water (100 mL), brine (100 mL), dried over Na2SO4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 95:5 hexane:ethyl acetate to afford 4,5-dimethyl-2-(phenylethynyl)-1,3-thiazole (338 mg 24% yield) as a white solid. M.p. 55-60°C. 1H NMR (CDCl3, 300 MHz) δ 7.56-7.53 (m, 2H), 7.35-7.33 (m, 3H), 2.38 (s, 6H). MS (ESI) 214.0 (M++H).

Example 58

5-Methyl-3-[(E)-2-phenylethenyl]-1,2,4-oxadiazole

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of (2E)-N-Hydroxy-3-phenyl-2-propenimidamide: To a solution of hydroxylamine hydrochloride (690 mg, 10 mmol) in ethanol was added NaOH (400 mg, 10 mmol),

followed by cinnamonitrile (1.3 g, 10 mmol). This mixture was heated to reflux for 16 h. The ethanol was removed *in vacuo*, the residue was acidified with 3M HCl (5 mL) and the solution was boiled for 30 minutes. The cooled solution was made basic (pH 8) with NH_4OH, and partitioned between water and ethyl acetate. The organics were concentrated to give a sticky white mass which was used without further purification.

Preparation of 5-Methyl-3-[(E)-2-phenylethenyl]-1,2,4-oxadiazole: (2*E*)-*N*-Hydroxy-3-phenyl-2-propenimidamide (1.6 g, 10 mmol) was mixed with excess acetyl chloride (30 mL), and heated to reflux. After 1 h the solution was cooled and the excess acetyl chloride was removed *in vacuo*. The resultant solids were triturated in hot ethyl acetate-hexane-acetone solution, and the supernatant was removed. The remaining solids were dried under high vacuum to afford 5-methyl-3-[(*E*)-2-phenylethenyl]-1,2,4-oxadiazole (0.50 g, 27% yield from cinnamonitrile) as a pale yellow powder. M.p. 166-168°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.59 (m, 3H), 7.42 (m, 3H), 6.58 (d, J=16 Hz, 1H), 2.17 (s, 3H).

Example 59

5-[(E)-2-phenylethenyl]-1,2,4-oxadiazole

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of *N*-[(Dimethylamino)methylene]-cinnamamide: Cinnamamide (4.4 g, 30 mmol) and *N,N*-dimethylformamide dimethylacetal (9.9 mL, 75 mmol) were heated at reflux for 2 h. Excess formamide and methanol formed in the reaction were removed *in vacuo*. The solids which formed were collected and washed with hexane, followed by two portions of ethyl acetate, then dried under vacuum at 40° C to afford *N*-[(dimethylamino)methylene]-cinnamamide (3.5 g, 58% yield) as a white crystalline solid. M.p. 91-93°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (s, 1H), 7.83 (d, J=16 Hz, 1H), 7.57 (m, 2H), 7.36 (m, 3H), 6.74 (d, J=16 Hz, 1H), 3.18 (m, 6H).

Preparation of *N*-[(Hydroxyamino)methylene]-cinnamamide: *N*-[(Dimethylamino)methylene]-cinnamamide (1.0 g, 5.0 mmol) was added to a solution of hydroxylamine hydrochloride (415 mg, 6.0 mmol) in acetic acid (5 mL of 70% aqueous) and aqueous NaOH (1.2 mL, 5 M, 6.0 mmol). After stirring for 1.5 h water (5 mL) was added , and the reaction mixture was cooled to 5° C in an ice bath. The solution was partitioned between ethyl acetate and water, and the organics were dried over Na_2SO_4, then concentrated *in vacuo* to afford *N*-[(hydroxyamino)methylene]-cinnamamide (850 mg, 90%). This material was carried on to the next step without further purification.

Preparation of 5-[(E)-2-phenylethenyl]-1,2,4-oxadiazole: N-[(Hydroxyamino)methylene]-cinnamamide (850 mg, 4.5 mmol) was dissolved in acetic acid/dioxane (20 mL 1:1 v:v), and heated to reflux for 2 h. The cooled solution was made basic (pH 8) with K_2CO_3, and partitioned between ethyl acetate and water. The organics were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant solids were triturated with hot ethyl acetate, and the soluble portion was purified by flash column chromatography on silica eluting with 2:1 hexane:ethyl acetate to afford 5-[(E)-2-phenylethenyl]-1,2,4-oxadiazole (60 mg, 8% yield) as a white powder. M.p. 53-55°C. 1H NMR (CDCl3, 300 MHz) δ 8.43 (s, 1H), 7.85 (d, J=16 Hz, 1H), 7.60 (m, 2H), 7.45 (m, 3H), 7.05 (d, J=16 Hz, 1H). MS (EI ionization) 171 (M^+-H).

Example 60

Preparation of 1-Methyl-5-[(E)-2-phenylethenyl]-1H-1,2,4-triazole

N-[(Dimethylamino)methylene]-cinnamamide (2.0 g, 10 mmol) was added to a mixture of acetic acid (20 mL) and methylhydrazine (0.6 mL, 11 mmol). The mixture was heated to 90° C for 2 h. The cooled mixture was concentrated *in vacuo*, and made basic (pH 9) with solid K_2CO_3. The aqueous residue was partitioned between ethyl acetate and water, the organics were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant powder was recrystallized from a minimum of boiling Ethyl acetate. The collected solids were triturated and washed with ethyl acetate to afford 1-methyl-5-[(*E*)-2-phenylethenyl]-1*H*-1,2,4-triazole (0.9 g, 49 % yield) as a pale yellow powder. M.p. 67-70°C from Ethyl acetate. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (s, 1H), 7.73 (d, J=16 Hz, 1H), 7.57 (m, 2H), 7.39 (m, 3H), 6.92 (d, J=16Hz, 1H), 3.96 (s, 3H).

Example 61

3-Methyl-5-[(E)-2-phenylethenyl]-1H-1,2,4-triazole

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of N-[(Dimethylamino)ethylidene]-cinnamamide: Cinnamamide (1.8 g, 12 mmol) and *N,N*-dimethylacetamide dimethylacetal (2.8 mL, 19 mmol) were heated to 120° C for 2 h. Excess amide and methanol formed in the reaction were removed *in vacuo*. The resultant material was purified by flash column chromatography on silica eluting with ethyl acetate to afford *N*-[(dimethylamino)ethylidene]-cinnamamide (2.1 g, 78 % yield) as a pale yellow solid containing one equivalent of ethyl acetate. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.61 (d, J=16 Hz, 1H), 7.53 (m, 2H), 7.36 (m, 3H), 6.68 (d, J=16 Hz, 1H), 3.13 (app d, J=15 Hz, 6H), 2.30 (s, 3H).

Preparation of 3-Methyl-5-[(E)-2-phenylethenyl]-1H-1,2,4-triazole: N-[(Dimethylamino)ethylidene]-cinnamamide (2.0 g, 9.0 mmol) was added to a solution of hydrazine hydrate (0.59 mL, 10 mmol) and acetic acid (25 mL). The mixture was heated to 90°C for 3 h, cooled,

and concentrated *in vacuo*. The resulting material was basified (pH 8) with solid K_2CO_3, and partitioned between ethyl acetate and water. The organics were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant material was purified by flash column chromatography on silica eluting with 1:2 hexane-ethyl acetate to afford 3-methyl-5-[(*E*)-2-phenylethenyl]-1*H*-1,2,4-triazole (1.6 g, 96% yield) as a white powder. M.p. 131-134°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, J=16 Hz, 0.3H), 7.59 (d, J=16 Hz, 0.7H), 7.49 (m, 2H), 7.32 (m, 3H), 7.05 (d, J=16 Hz, 1H), 6.49 (d, J=16 Hz, 0.4H), 6.21 (br s, 0.3H), 5.88 (br s, 0.3H), 2.53 (s, 3H). MS (EI ionization) 184 (M^+-H).

Example 62

Ethyl 3-[(E)-2-phenylethenyl]-1,2,4-thiadiazole-5-carboxylate

The title compound was prepared in several steps, with the preparation of key intermediates set forth herein as follows:

Preparation of 5-[(E)-2-Phenylethenyl]-1,3,4-oxathiazol-2-one: Cinnamamide (1.9 g, 13 mmol) was mixed with chlorocarbonylsulphenylchloride (1.0 mL, 13 mmol) in chloroform and heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the resultant material was taken up in boiling hexane (100 mL). The solvent was decanted from the remaining solid, the volume of this solution was reduced by half, and the solution was allowed to cool. The crystalline solids which formed were collected and washed with hexane to afford 5-[(*E*)-2-phenylethenyl]-1,3,4-oxathiazol-2-one (1.93 g, 72% yield) as pale yellow needles. M.p. 105-106°C ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.52 (m, 3H), 7.46 (s, 0.5H), 7.41 (m, 2.5H), 6.63 (d, J=16 Hz, 1H).

Preparation of Ethyl 3-[(E)-2-phenylethenyl]-1,2,4-thiadiazole-5-carboxylate: 5-[(*E*)-2-Phenylethenyl]-1,3,4-oxathiazol-2-one (1.4 g, 7.0 mmol) was mixed with ethyl cyanoformate (2.4 g, 25 mmol) in xylenes, and heated to reflux for 3 h. The reaction mixture was concentrated *in vacuo*, and the resulting material was recrystallized from ethyl acetate-ethanol (1:1) to give ethyl 3-[(*E*)-2-phenylethenyl]-1,2,4-thiadiazole-5-carboxylate (1.2 g, 66% yield) as a light yellow solid. M.p. 79-80°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, J=16 Hz, 1H), 7.61 (m, 2H), 7.40 (m, 3H), 7.29 (d, J=11 Hz, 1H), 4.56 (q, J=7 Hz, 2H), 1.50 (t, J=7 Hz, 3H). MS (EI ionization) 259 (M^+-H).

Example 63

{3-[(E)-2-phenylethenyl]-1,2,4-thiadiazol-5-yl}methanol

Ethyl 3-[(*E*)-2-phenylethenyl]-1,2,4-thiadiazole-5-carboxylate (1.0 g, 3.8 mmol) was suspended in methanol (50 mL), and $NaBH_4$ (220 mg, 5.8 mmol) was added in portions. The mixture was stirred for 16 h at ambient temperature. The reaction was concentrated *in vacuo*, acidified with aqueous HCl (4 M) to pH 2, and partitioned between Ethyl acetate and water. The organics were dried over Na_2SO_4, concentrated *in vacuo*, and the resultant material was rerystallized from ethyl acetate to afford {3-[(*E*)-2-phenylethenyl]-1,2,4-thiadiazol-5-yl}methanol (0.6 g, 71% yield) as a pale yellow solid. M.p. 119-

120°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J=16 Hz, 1H), 7.57 (m, 2H), 7.38 (m, 3H), 7.23 (d, J=16 Hz, 1H), 5.14 (d, J=5 Hz, 2H), 3.29 (t, J=5 Hz, 1H). MS (EI ionization) 217 (M^+-H).

Example 64

2-(1-Cyclohexen-1-ylethynyl)-5-methylthiophene

2-Iodo-5-methylthiophene (1.0 g, 4.5 mmol) was mixed with $PdCl_2$ (44 mg, 0.25 mmol), PPh_3 (200 mg, 0.75 mmol), CuI (140 mg, 0.75 mmol) and K_2CO_3 (1.66 g, 12 mmol) in a solution of DME and water (1:1). Argon gas was bubbled through the suspension for twenty minutes to deoxygenate the mixture. 1-Ethynyl-1-cyclohexene (1.06 g, 10.0 mmol) was added and the mixture was heated to reflux. After 16 hours the reaction was cooled and filtered through Celite™. The resultant solution was partitioned between water and ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting product was purified by flash column chromatography on silica gel eluting with hexane to afford 2-(1-cyclohexen-1-ylethynyl)-5-methylthiophene (0.96 g, 86% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (d, J= 3.5 Hz, 1H), 6.60 (m, 1H), 6.18 (m, 1H), 2.45 (s, 3H), 2.13 (m, 4H), 1.68-1.57 (m, 4H). MS (EI ionization) 202 (M^+).

Example 65

Synthesis of 2-(1*H*-inden-2-ylethynyl)pyridine

2-Indanone (1.0g, 7.6 mmol) was dissolved in THF (60 mL) and cooled to –78°C in an argon blanketed flask. Potassium hexamethyl disilazide (9.1 mmol, 18.2 mL of a 0.5M solution in toluene) was added dropwise to this stirred solution. After 30 min, *N*-phenyl trifluoromethanesulfonimide (4.05 g, 11.4 mmol) was added as a solution in THF (15 mL). The reaction was stirred for 15 min at –78°C, then brought to ambient temperature and stirred for an additional 1 h, after which time it was quenched with H_2O (15 mL) and diluted with ethyl acetate (500 mL). The ethyl acetate solution was washed with H_2O (3 x 100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with 30:1 hexanes:ethyl acetate to afford 2-[(trifluoromethyl)sulfonyl]-1*H*-indene (1.28 g, 64% yield) as a brown oil. The enol triflate (500 mg, 1.89 mmol) and 2-ethynyl pyridine (579 mg, 5.62 mmol) were dissolved in DME (10 mL) and deoxygenated via argon bubbling for 20 min and then added via syringe to a deoxygenated DME (25 mL) solution of triphenylphosphine (100 mg, 0.38 mmol), *bis*-triphenylphosphine palladium dichloride (133 mg, 0.19 mmol), CuI (72 mg, 0.38 mmol), and triethylamine (954 mg, 1.32 mL, 9.45 mmol). The reaction was capped with a reflux condenser and stirred at 80°C for 1.5 h, after which time it was cooled to ambient temperature and poured in to a separatory funnel containing ethyl acetate (300 mL), where it was washed with H_2O (2 x 100 mL) and brine (100 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 6:1 hexanes:ethyl acetate to afford 2-(1*H*-inden-2-ylethynyl)pyridine (309 mg, 75% yield) as the free base, which was then solubilized in diethyl ether (25 mL) and precipitated as the

hydrochloride salt (M.p. 170-172°C) upon treatment with 1M HCl in diethyl ether (5 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.98 (d, J=5.7 Hz, 1H), 8.76 (t, J=8.0 Hz, 1H), 8.33 (d, J=8.0 Hz, 1H), 8.17 (t, J=6.3 Hz, 1H), 7.82 (s, 1H), 7.72 (m, 2H), 7.53 (m, 2H), 3.96 (s, 2H). MS (ESI) 218.1 (M^++H).

Example 66

Synthesis of 2-(3,4-dihydro-2-naphthalenylethynyl)pyridine

2,6-Lutidine (547 mg, 594 µL, 5.1 mmol) was added neat, via syringe to a stirred, argon blanketed solution of β-tetralone (500 mg, 3.4 mmol) in methylene chloride (30 mL) at ambient temperature. After 5 min, trifluoromethanesulfonic anhydride (1.439 g, 858 µL, 5.1 mmol) was added slowly via syringe. After 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and partitioned between ethyl acetate (200 mL) and H_2O (50 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was then chromatographed on silica gel, eluting with 20:1 hexanes:ethyl acetate to afford 3-[(trifluoromethyl)sulfonyl]-1,2-dihydronaphthalene (361 mg, 38% yield) as a brown oil. Following the procedure described for Example 65, the β-tetralone enol triflate (275 mg, 1.0 mmol) was cross-coupled with 2-ethynylpyridine (337 mg, 3.27 mmol) in a reaction over 16 h at 70°C. Upon completion, the reaction was concentrated *in vacuo*, and the residue was chromatographed on silica gel, eluting with 7:1 hexanes:ethyl acetate to afford 2-(3,4-dihydro-2-naphthalenylethynyl)pyridine (193 mg, 84% yield) as an off white semi-solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.62 (d, J=4.5 Hz, 1H), 7.67 (ddd, J=7.7 Hz, 7.7 Hz, 1.8 Hz, 1H), 7.48 (d, J=7.9 Hz, 1H), 7.07-7.28 (m, 5H), 7.00 (s, 1H), 2.91 (t, J=7.8 Hz, 2H), 2.59 (t, J=8.4 Hz, 2H). MS (ESI) 232.1 (M^++H).

Example 67

Synthesis of 1-(2-pyridinylethynyl)-1-indanol

n-Butyllithium (18.93 mmol, 11.8 mL of 1.6M solution in hexanes) was added dropwise to a stirred solution of 2-ethynylpyridine (1.95 g, 18.93 mmol) in THF (80 mL) at –78°C. After 15 min, solid anhydrous $CeCl_3$ (4.66 g, 18.93 mmol) was added and the reaction was stirred for an additional 1 h, at which time a solution of 1-indanone (1.00 g, 7.57 mmol) in THF (10 mL) was added via syringe. The reaction was then warmed to ambient temperature, stirred for 1 h, and quenched with 5 mL H_2O. The reaction was then diluted with ethyl acetate (250 mL) and extracted with H_2O (3 x 75 mL). The combined aqueous portions were back-extracted with ethyl acetate (100 mL). The ethyl acetate layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1:1 hexanes:ethyl acetate to afford 1-(2-pyridinylethynyl)-1-indanol (1.1 g, 62% yield) as a thick amber liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (d, J=4.9 Hz, 1H), 7.63 (d, J=6.6 Hz, 1H), 7.54 (ddd, J=7.7 Hz, 7.7 Hz, 1.7 Hz, 1H), 7.33 (d, J=7.8 Hz, 1H), 7.10-7.25 (m, 4H), 5.50 (s, 1H), 3.12 (m, 1H), 2.91 (m, 1H), 2.68 (m, 1H), 2.53 (m, 1H). MS (ESI) 236.1 (M^++H).

Example 68

Synthesis of 1-fluoro-2-(2-pyridinylethynyl)-2-indanol

Potassium hexamethyldisilazide (19.9 mmol, 39.8 mL of 0.5M solution in toluene) was added slowly to a stirred solution of 2-indanone (2.20 g, 16.6 mmol) in THF (60 mL) at –78°C. After 15 min, trimethylsilyl chloride (2.64 mL, 20.8 mmol) was added to generate the 1*H*-inden-2-yl trimethylsilyl ether. The reaction was stirred for 10 min at –78°C, then brought to ambient temperature and stirred for an additional 30 min, after which time the solvents were removed *in vacuo* and replaced with anhydrous acetonitrile (80 mL). Solid Selectfluor™ (8.82 g, 24.9 mmol) reagent was then added and the resulting slurry was stirred for 16 h at ambient temperature. The reaction was then diluted with ethyl acetate (400 mL) and extracted with H_2O (3 x 100 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with 4:1 hexanes:ethyl acetate to afford the 1-fluoro-2-indanone (1.05 g, 42% yield) product as a sticky brown solid. Following the procedure outlined for Example 67, the intermediate 1-fluoro-2-indanone (1.05 g, 7.0 mmol) was cross-coupled with 2-ethynyl pyridine (1.44 g, 14.0 mmol) to afford 1-fluoro-2-(2-pyridinylethynyl)-2-indanol (320 mg, 18% yield, 8% overall yield) as a tan semi-solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, J=4.8 Hz, 1H), 7.64 (ddd, J=7.8 Hz, 7.8 Hz, 1.8 Hz, 1H), 7.49 (d, J=7.3 Hz, 1H), 7.22-7.43 (m, 5H), 5.98 (d, $J[^1H\text{-}^{19}F]$ = 56.0 Hz, 1H), 4.29 (s, 1H), 3.51 (s, 2H). MS (ESI) 254.1 (M^++H).

Example 69

Synthesis of 2-[(3-fluoro-1*H*-inden-2-yl)ethynyl]pyridine

n-Butyllithium (2.39 mmol, 1.5 mL of 1.6M solution in hexanes) was added slowly to a stirred solution of 1-fluoro-2-(2-pyridinylethynyl)-2-indanol (550 mg, 2.17 mmol) and LiBr (188 mg, 2.17 mmol) in THF (15 mL) at –78°C. After 30 min, methanesulfonyl chloride (274 mg, 185 µL, 2.39 mmol) was added and the reaction was stirred for an additional 1.5 h at ambient temperature before quenching with H_2O (5 mL). The reaction flask contents were then transferred to a separatory funnel containing ethyl acetate (100 mL) that was subsequently washed with H_2O (2 x 50 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was then dissolved in methylene chloride (25 mL), treated with DBU (1.982 g, 1.947 mL, 13.02 mmol), and warmed to reflux. After 16 h, the reaction mixture was cooled to ambient temperature, diluted with methylene chloride (100 ml) and washed with H_2O (2 x 50 mL). The methylene chloride layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 5:1 hexanes:ethyl acetate to afford 2-[(3-fluoro-1*H*-inden-2-yl)ethynyl]pyridine (75 mg, 15% yield) as a yellow oil which was then solubilized in ether (15 mL) and precipitated as the hydrochloride salt (M.p. 150-152°C) upon treatment with 1M HCl in diethyl ether (2 mL). ^1H NMR (CD_3OD, 300 MHz) δ 8.81 (d, J=5.3 Hz, 1H), 8.59 (ddd, J=8.0 Hz, 8.0 Hz, 1.4 Hz, 1H), 8.16 (d, J=8.

Hz, 1H), 8.00 (dd, J=6.4 Hz, 6.4 Hz, 1H), 7.45-7.58 (m, 4H), 3.76 (d, $J[^1H-^{19}F]$ = 6.6 Hz). MS (ESI) 236.1 (M^++H).

Example 70

Synthesis of 2-[(*tert*-butoxycarbonyl)amino]benzoic acid

Anthranilic acid (1.37 g, 10.0 mmol) and di-*tert*-butyl dicarbonate (3.12 g, 14.3 mmol) were added to a stirred mixture of 0.5M NaOH (20.0 mL), dioxane (10.0 mL), and CH_3CN (2.0 mL) at 0°C. The cold bath was removed, and the reaction mixture was stirred at ambient temperature for 16 h before quenching with 10% aqueous citric acid (30 mL). The mixture was diluted with H_2O (100 mL) in a separatory funnel and extracted with methylene chloride (3 x 100 mL). The combined methylene chloride extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to obtain 2-[(*tert*-butoxycarbonyl)amino]benzoic acid (2.33 g, 98% yield) as a white solid that was suitably pure to carry on to the next synthetic step.

Example 71

Synthesis of *tert*-butyl 2-{[methoxy(methyl)amino]carbonyl}phenylcarbamate

To a stirred solution of the *N*-BOC-anthranilic acid from Example 70 (2.33 g, 9.8 mmol) in methylene chloride (100 mL) was added EDC (2.82 g, 14.7 mmol), hydroxybenzotriazole dihydrate (1.459 g, 10.8 mmol), diisopropyl ethylamine (6.0 mL, 34.3 mmol), and *N,O*-dimethylhydroxylamine hydrochloride (1.43 g, 14.7 mmol). The reaction was stirred for 16 h, after which time it was concentrated *in vacuo* and diluted with ethyl acetate (500 mL). The ethyl acetate solution was washed with 1M HCl (100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), and H_2O (2 x 100 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 4:1 hexanes:ethyl acetate to afford *tert*-butyl 2-{[methoxy(methyl)amino]carbonyl}phenylcarbamate (2.00 g, 73% yield) as a pale yellow solid.

Example 72

Synthesis of tert-butyl 2-formylphenylcarbamate

$LiAlH_4$ (6.67 mmol, 6.67 mL of a 1.0M solution in THF) was added to an Ar-purged, stirred solution of the *tert*-butyl 2-{[methoxy(methyl)amino]carbonyl}phenylcarbamate from Example 71 (1.87 g, 6.67 mmol) in THF (50 mL) at –78°C. Stirring was continued at –78°C for 15 min, after which time the reaction was brought to ambient temperature and stirred for an additional 1 h. The reaction was then cooled to 0°C and treated with 1N aqueous HCl (25 mL) to quench. The mixture was poured in to a separatory funnel containing H_2O (250 mL) and extracted with methylene chloride (3 x 100 mL). The combined methylene chloride layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford *tert*-butyl 2-formylphenylcarbamate (1.48 g, 100% yield) as a tan solid.

Example 73

Synthesis of tert-butyl 2-[1-hydroxy-3-(2-pyridinyl)-2-propynyl]phenylcarbamate

n-Butyllithium (14.0 mmol, 8.75 mL of 1.6M solution in hexanes) was added dropwise to a stirred solution of 2-ethynylpyridine (1.44 g, 14.0 mmol) in THF (80 mL) at –78°C. After 15 min, solid anhydrous $CeCl_3$ (3.45 g, 14.0 mmol) was added and the reaction was stirred for an additional 1 h, after which time a solution of the *tert*-butyl 2-formylphenylcarbamate from Example 72 (1.48 g, 6.7 mmol) in THF (20 mL) was added via syringe. The reaction was warmed to ambient temperature, stirred for 1 h, quenched with H_2O (5 mL), then diluted with ethyl acetate (250 mL) and extracted with H_2O (3 x 75 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, resulting in a crude residue that was chromatographed on silica gel, eluting with 2:1 hexanes:ethyl acetate to afford the racemic 2° alkanol (1.71 g, 79% yield) as a light peach colored amorphous solid.

Example 74

Synthesis of 4-(2-pyridinylethynyl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

The *tert*-butyl 2-formylphenylcarbamate from Example 73 (250 mg, 0.77 mmol) was deprotected without incident by dissolving the compound in dioxane (10 mL), treating it with 4M HCl in dioxane (30 mL, 120 mmol HCl), and stirring for 2.5 h, resulting in precipitation from solution of the 1-(2-aminophenyl)-3-(2-pyridinyl)-2-propyn-1-ol as the hydrochloride salt. The dioxane solvent was decanted, the precipitate was triturated with diethyl ether (3 x 20 mL) and dried *in vacuo* to obtain the crude deprotected material as a pale pink solid. The deprotection was assumed to be quantitative, and the crude material was therefore carried on to the next step, dissolving it in a solution of diisopropylethylamine (500 mg, 674μL, 3.87 mmol) in methylene chloride (20 mL). The reaction flask was cooled to 0°C, and phosgene (1.935 mmol, 1.02 mL of a 1.89M solution in toluene) was added dropwise to the stirred solution. Stirring at 0°C was continued for 2.5 h, followed by an H_2O (5 mL) quench. The biphasic mixture was diluted with ethyl acetate (100 mL) and washed with H_2O (2 x 50 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 2:1 hexanes:ethyl acetate to obtain 4-(2-pyridinylethynyl)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (140 mg, 73% yield) as a tan, semi-solid glass. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.13 (s, 1H), 8.61 (d, J=4.4 Hz, 1H), 7.69 (ddd, J=7.8 Hz, 7.8 Hz, 1.8 Hz, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.41 (d, J=7.6 Hz, 1H), 7.27-7.34 (m, 2H), 7.11 (ddd, J=7.6 Hz, 7.6 Hz, 0.8 Hz, 1H), 6.93 (d, J=7.8 Hz, 1H), 6.34 (s, 1H). MS (ESI) 251.1 (M^++H).

Example 75

Synthesis of ethyl 3-(2-pyridinylethynyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

N-Carbethoxy-4-tropinone (500 mg, 2.54 mmol) was dissolved in THF (25 mL) and cooled to –78°C in an argon blanketed flask. Potassium hexamethyldisilazide (3.05 mmol, 6.1 mL of a 0.5M solution in toluene) was added dropwise to this stirred solution. After 15 min, *N*-phenyl

trifluoromethanesulfonimide (1.36 g, 3.81 mmol) was added as a solution in THF (10 mL). The reaction was stirred for 15 min at –78°C, then brought to ambient temperature and stirred for an additional 1 h, after which time it was quenched with H_2O (10 mL) and diluted with ethyl acetate (200 mL). The ethyl acetate solution was washed with H_2O (3 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with a gradient from 5% to 50% ethyl acetate in hexanes to afford the ethyl 3-[(trifluoromethyl)sulfonyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (820 mg, 98% yield) as a tan liquid. The ethyl 3-[(trifluoromethyl)sulfonyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (820 mg, 2.50 mmol) and 2-ethynylpyridine (516 mg, 5.00 mmol) were dissolved in DME (15 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated DME (25 mL) solution of triphenylphosphine (131 mg, 0.50 mmol), *bis*-triphenylphosphine palladium dichloride (176 mg, 0.25 mmol), CuI (95 mg, 0.50 mmol), and triethylamine (1.265 g, 1.74 mL, 12.50 mmol). The reaction was warmed to 50°C and stirred for 1.5 h, after which time it was cooled to ambient temperature and poured into a separatory funnel containing ethyl acetate (350 mL), where it was washed with H_2O (2 x 100 mL) and brine (100 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1:1 hexanes:ethyl acetate to afford ethyl 3-(2-pyridinylethynyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (400 mg, 57% yield) as a free base. The toluenesulfonate salt was then prepared by adding solid toluenesulfonic acid to a solution of ethyl 3-(2-pyridinylethynyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (200 mg, 0.69 mmol) in ethanol (10 mL). The mixture was stirred for 5 min until all solids were dissolved, after which time the solution was concentrated *in vacuo*. The resulting red oil was triturated with ether (3 x 10 mL) and placed under high vacuum, where it foamed to a dark red semi-solid. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.86 (d, J=5.3 Hz, 1H), 8.64 (ddd, J=8.0 Hz, 8.0 Hz, 1.5 Hz, 1H), 8.16 (d, J=8.1 Hz, 1H), 8.07 (dd, J=6.3 Hz, 1H), 7.80 (d, J=8.2 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 6.96 (d, J=5.3 Hz, 1H), 4.64 (m, br., 1H), 4.52 (m, br., 1H), 4.24 (q, J=7.0 Hz, 2H), 2.92-3.08 (m, br., 1H), 2.45 (s, 3H), 2.07-2.41 (m, 4H), 1.86 (m, br., 1H), 1.36 (t, J=7.0, 3H). MS (ESI) 283.2 (M^++H).

Example 76

Synthesis of 1-chloro-4-(trimethylsilyl)-3-butyn-2-one

Aluminum trichloride (21.9 g, 164 mmol) was suspended in CH_2Cl_2 (250 mL) and cooled in an ice bath. Bis(trimethylsilyl)acetylene (20.0 g, 117 mmol) and chloroacetyl chloride (10.3 mL, 129 mmol) were combined in CH_2Cl_2 (150 mL) and the solution was added to the $AlCl_3$ suspension dropwise from an addition funnel over 1 h. The dark brownish-red solution was stirred at 0°C for 1 h, then the ice bath was removed. After 1 h at ambient temperature, the reaction was cooled to 0°C and quenched by slow addition of 1M HCl (250 mL). The acidic solution was extracted with CH_2Cl_2 (2 x 500 mL), the combined organic layers were washed with H_2O (500 mL), $NaHCO_3$ (500 mL), brine (500 mL) and dried over Na_2SO_4. The organic layer was treated with silica gel, and filtered to afford a clear

solution which was concentrated *in vacuo*. The residue was distilled under high vacuum through a vigreaux column. The main part of the distillate was collected at a head temperature of 58°C (the lower thermometer was 68°C) to afford 1-chloro-4-(trimethylsilyl)-3-butyn-2-one (11.25 g, 54% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.24 (s, 2H), 0.28 (d, 9H).

Example 77

Synthesis of 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole

The 1-chloro-4-(trimethylsilyl)-3-butyn-2-one from Example 76 (10 g, 57.2 mmol) was dissolved in DMF (100 mL), then thioacetamide (5.6 g, 74 mmol) was added in one portion. The mixture was allowed to stir for 16 h at ambient temperature, at which time TLC showed no remaining 1-chloro-4-(trimethylsilyl)-3-butyn-2-one. The mixture was diluted with ethyl acetate (400 mL), and washed with H_2O (3 x 300 mL), brine (300 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with hexane, 98:2, then 96.5:3.5 hexane:ethyl acetate to afford 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole (8.0 g, 72% yield) as reddish-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 1H), 2.70 (s, 3H), 0.26 (s, 9H). MS (EI ionization)195 (M^+).

Example 78

Synthesis of 4-[(trimethylsilyl)ethynyl]-1,3-thiazol-2-ylamine

The 1-chloro-4-(trimethylsilyl)-3-butyn-2-one from Example 76 (4.25 g, 24.3 mmol) was dissolved in DMF (20 mL), then thiourea (2.45 g, 32.2 mmol) was added in one portion. The mixture was allowed to stir for 16 h at ambient temperature, at which time TLC showed no remaining 1-chloro-4-(trimethylsilyl)-3-butyn-2-one. The mixture was diluted with ethyl acetate (200 mL), and washed with H_2O (3 x 200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with hexane, 9:1, then 4:1 hexane:ethyl acetate to afford 4-[(trimethylsilyl)ethynyl]-1,3-thiazol-2-ylamine (4.1 g, 86% yield) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.70 (s, 1H), 5.47 (br s, 2H), 0.20 (s, 9H). MS (EI ionization) 196 (M^+).

Example 79

Synthesis of 4-[(2-methyl-1,3-thiazol-4-yl)ethynyl]isoquinoline

4-Bromoisoquinoline (276 mg, 1.33 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (200 mg, 1.02 mmol) were dissolved in DMF (5 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated, 40°C DMF (15 mL) solution of triphenylphosphine (71 mg, 0.27 mmol), *bis*-triphenylphosphine palladium dichloride (93 mg, 0.13 mmol), CuI (51 mg, 0.27 mmol), tetrabutylammonium iodide (377 mg, 1.02 mmol), and triethylamine (515 mg, 710 µL, 5.1 mmol). The reaction mixture was warmed to 60°C, and

tetrabutylammonium fluoride (1.33 mmol, 1.33 mL of a 1.0 M solution in THF) was added slowly over 1.5 h. The reaction was then cooled to ambient temperature and poured into a separatory funnel containing 1:1 hexanes:ethyl acetate (200 mL) where it was washed with 50% dilute brine (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1.5:1 hexanes:ethyl acetate to afford 4-[(2-methyl-1,3-thiazol-4-yl)ethynyl]isoquinoline (195 mg, 76% yield) as an off-white solid that was then solubilized in ether (15 mL) and precipitated as the white hydrochloride salt (M.p. 209-210°C) upon treatment with 1M HCl in diethyl ether (5 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 9.85 (s, 1H), 8.93 (s, 1H), 8.73 (d, J=8.4 Hz, 1H), 8.64 (d, J=8.4 Hz, 1H), 8.42 (ddd, J=7.2 Hz, 7.2 Hz, 1.1 Hz, 1H), 8.17 (dd, J=7.1 Hz, 7.1 Hz, 1H), 8.16 (s, 1H), 2.85 (s, 3H). MS (ESI) 251.1 (M^++H).

Example 80

Synthesis of 4-(4-isoquinolinylethynyl)-1,3-thiazol-2-amine

Following the procedure and mole equivalents indicated for Example 79, 4-bromoisoquinoline (691 mg, 3.32 mmol) and 4-[(trimethylsilyl)ethynyl]-1,3-thiazol-2-amine from Example 78 (500 mg, 2.55 mmol) were cross-coupled to obtain 4-(4-isoquinolinylethynyl)-1,3-thiazol-2-amine (262 mg, 41% yield) as a tannish-orange solid after eluting with 2:1 hexanes:ethyl acetate from a silica gel column. This material was then solubilized in ether (15 mL) and precipitated as the yellow hydrochloride salt (M.p. >150°C, dec.) upon treatment with 1M HCl in diethyl ether (5 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 9.85 (s, 1H), 8.96 (s, 1H), 8.69 (d, J=8.4 Hz, 1H), 8.62 (d, J=8.3 Hz, 1H), 8.40 (ddd, J=7.1 Hz, 7.1 Hz, 1.2 Hz, 1H), 8.16 (dd, J=8.1 Hz, 8.1 Hz, 1H), 7.58 (s, 1H). MS (ESI) 252.0 (M^++H).

Example 81

Synthesis of 2-[(trimethylsilyl)ethynyl]pyrimidine

$PdCl_2$ (166 mg, 0.93 mmol), CuI (481 mg, 2.52 mmol), and triethylamine (18 mL, 129 mmol) were combined in DME (50 mL) under argon. Argon gas was bubbled through the resulting dark suspension while it was warmed to 70°C in an oil bath. Triphenylphosphine (978 mg, 3.73 mmol) was added and the argon flow was continued for 10 min. The argon flow was discontinued, the heating bath was removed, and 2-bromopyrimidine (5.14 g, 32.3 mmol), and trimethylsilylacetylene (9.1 mL, 64 mmol), were added as a solution in DME (30 mL) followed by a rinse of the flask and syringe with DME (10 mL). Solids appeared in the flask after the addition was completed. The reaction mixture was then heated to 45°C. After 1 h the heating was discontinued and the reaction mixture was allowed to cool to ambient temperature. After 16 h at ambient temperature TLC analysis showed no starting 2-bromopyrimidine present. The reaction mixture was concentrated *in vacuo*, diluted with diethylether (300 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a dark oil which partially solidified when pumped down under high vacuum. The crude product was purified by column

chromatography eluting with hexane, 9:1, 8:1, 6:1, 4:1, then 3:1 hexane:ethyl acetate to afford 2-[(trimethylsilyl)ethynyl]pyrimidine (5.2 g, 91 % yield) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (d, J=4.9 Hz, 2H), 7.25 (m, 1H), 0.30 (s, 9H). MS (EI ionization) 176 (M^+).

Example 82

Synthesis of 4-(2-pyrimidinylethynyl)isoquinoline

4-Bromoisoquinoline (499 mg, 2.40 mmol) and 2-[(trimethylsilyl)ethynyl]pyrimidine from Example 81 (352 mg, 2.00 mmol) were dissolved in DMF (10 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated solution of triphenylphosphine (84 mg, 0.32 mmol), *bis*-triphenylphosphine palladium dichloride (112 mg, 0.16 mmol), CuI (61 mg, 0.32 mmol), tetrabutylammonium iodide (369 mg, 1.00 mmol), and triethylamine (1.01 g, 1.39 mL, 10.00 mmol) in DMF (20 mL) at 40°C. The reaction was warmed to 50°C, and tetrabutylammonium fluoride (2.10 mmol, 2.10 mL of a 1.0M solution in THF) was added slowly over 1.5 h. The reaction was then cooled to ambient temperature and poured in to a separatory funnel containing 1:1 hexanes:ethyl acetate (200 mL) where it was washed with 50% dilute brine (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1.5:1 hexanes:ethyl acetate to afford 4-(2-pyrimidinylethynyl)isoquinoline (210 mg, 45% yield) as an off-white solid that was then solubilized in diethyl ether (15 mL) and precipitated as the tan hydrochloride salt (M.p. 158-159°C) upon treatment with of 1M HCl in diethyl ether (3 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 9.95 (s, 1H), 9.06 (s, 1H), 8.99 (d, J=5.0 Hz, 2H), 8.75 (d, J=8.4 Hz, 1H), 8.67 (d, J=8.3 Hz, 1H), 8.42 (ddd, J=7.2 Hz, 7.2 Hz, 1.1 Hz, 1H), 8.17 (dd, J=7.3 Hz, 7.3 Hz, 1H), 7.67 (dd, J=5.0 Hz, 5.0 Hz, 1H). MS (ESI) 232.0 (M^++H).

Example 83

Synthesis of 2-[(6,7-dimethoxy-3,4-dihydro-2-naphthalenyl)ethynyl]pyridine

Using the procedure described in Example 66 but using 6,7-dimethoxy-1-tetralone in place of β-tetralone, 6,7-dimethoxy-3,4-dihydro-1-naphthalenyl trifluoromethanesulfonate was prepared in 90% yield. 6,7-Dimethoxy-3,4-dihydro-1-naphthalenyl trifluoromethanesulfonate (1.48 g) was cross-coupled with 2-ethynylpyridine without incident following the procedure described for Example 66. The crude reaction material was chromatographed on silica gel, eluting the product with 2:1 hexanes:ethyl acetate to obtain 2-(6,7-dimethoxy-3,4-dihydro-1-naphthalenylethynyl)pyridine (265 mg, 40% overall yield, 2 steps) as a pale yellow solid that was then solubilized in diethyl ether (15 mL) and precipitated as the yellow-orange hydrochloride salt upon treatment with of 1M HCl in diethyl ether (5 mL). M.p. 148-150°C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.76 (d, J=5.7 Hz, 1H), 8.52 (ddd, J=7.9 Hz, 7.9 Hz, 1.5 Hz, 1H), 8.14 (d, J=8.0 Hz, 1H), 7.94 (dd, J=6.3 Hz, 6.3 Hz, 1H), 7.11 (s, 1H), 6.80 (t, J=5.0 Hz, 1H), 6.79 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.74 (t, J=8.2 Hz, 2H), 2.43 (m, 2H). MS (ESI) 292.1 (M^++H).

Example 84

Synthesis of methyl 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]nicotinate

Concentrated sulfuric acid (18 mL) was added to a stirred solution of 5-bromonicotinic acid (10.1 g, 50.0 mmol) in methanol (300 mL). The reaction was warmed to reflux and stirred for 18 h, then cooled to ambient temperature and quenched with saturated $NaHCO_3$, adjusting the pH to ~9. The methanol was removed *in vacuo*, and the remaining aqueous mixture was further diluted with H_2O (250 mL) and extracted with ethyl acetate (3 x 100 mL). The ethyl acetate layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to obtain methyl 5-bromonicotinate (10.09 g, 93% yield) as a white crystalline solid (M.p. = 98-99°C) without further purification. This material (3.02 g, 14.0 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (2.48 g, 12.7 mmol) were dissolved together in DMF (20 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated, 40°C DMF (60 mL) solution of triphenylphosphine (534 mg, 2.04 mmol), *bis*-triphenylphosphine palladium dichloride (713 mg, 1.02 mmol), CuI (388 mg, 2.04 mmol), tetrabutylammonium iodide (1.88 g, 5.08 mmol), and triethylamine (6.414 g, 8.8 mL, 63.5 mmol). The reaction was warmed to 50°C, and tetrabutylammonium fluoride (14.0 mmol, 14.0 mL of a 1.0M solution in THF) was added via syringe pump over 1.5 h. The reaction was then cooled to ambient temperature and poured into a separatory funnel containing 1:1 hexanes:ethyl acetate (400 mL) where it was washed with 50% dilute brine (3 x 100 mL). The aqueous portion was back-extracted with 1:1 hexanes:ethyl acetate (100 mL). The organic layers were then combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the crude residue was chromatographed on silica gel, eluting with 3:1 hexanes:ethyl acetate to afford methyl 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]nicotinate (2.56 g, 78% yield) as an off-white solid. M.p. = 124-125°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.15 (s, 1H), 8.93 (s, 1H), 8.40 (dd, J= 2.0 Hz, 2.0 Hz, 1H), 7.49 (s, 1H), 3.98 (s, 3H), 2.76 (s, 3H). MS (ESI) 259.0 (M^++H).

Example 85

Synthesis of *N*-hydroxyethanimidamide hydrochloride

Hydroxylamine hydrochloride (13.8 g, 200 mmol) was dissolved in a 1M solution of NaOH in ethanol (200 mL). To this was added acetonitrile (8.2 g, 10.43 mL, 200 mmol) neat, via syringe. The reaction was stirred at reflux for 17 h, then cooled to ambient temperature at which time 12M HCl was added (35.4 mL, 425 mmol). The mixture was concentrated *in vacuo* to afford a white solid to which was added boiling ethanol (200 ml). The insoluble material was then filtered, and the filtrate was collected and concentrated *in vacuo* to obtain *N*-hydroxyethanimidamide hydrochloride (19.45 g, 88% yield) as a white crystalline solid.

Example 86

Synthesis of 3-(3-methyl-1,2,4-oxadiazol-5-yl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

NaH (23.4 mmol, 936 mg of a 60% suspension in mineral oil) was added to a suspension of *N*-hydroxyethanimidamide hydrochloride from Example 85 (1.27 g, 11.5 mmol) in THF (50 mL). The mixture was warmed to 50°C and stirred for 30 min, after which time methyl 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]nicotinate from Example 84 (1.00g, 3.9 mmol) was added as a solution in THF (20 mL). After 45 min, the reaction was quenched with H_2O (15 mL), and partitioned between ethyl acetate (250 mL) and H_2O (100 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was filtered through a short plug of silica gel, eluting with 2.5% methanol in methylene chloride, then recrystallized from 1:1 hexanes:ethyl acetate to obtain 3-(3-methyl-1,2,4-oxadiazol-5-yl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (596 mg, 54% yield) as white crystalline leaves, M.p. 153-154°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.27 (d, J=2.0 Hz, 1H), 8.95 (d, J=2.0 Hz, 1H), 8.52 (dd, J=2.0 Hz, 2.0 Hz, 1H), 7.50 (s, 1H), 2.77 (s, 3H), 2.51 (s, 3H). MS (ESI) 283.0 (M^++H).

Example 87

Synthesis of 1-(methylsulfonyl)-3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-1H-indole

To a vigorously stirred solution of indole (1.0 g, 8.6 mmol) in DMF (40 mL) at ambient temperature was added KOH pellets (1.8 g, 32.1 mmol) followed by iodine (4.34 g, 17.1 mmol). After 15 min, the reaction was poured in to a separatory funnel containing saturated aqueous sodium thiosulfate (200 mL), which was then extracted with 1:1 hexanes:ethyl acetate (3 x 100 mL). The combined organic layers were first back-extracted with 1:1 H_2O:brine (3 x 75 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude 3-iodo-1*H*-indole product was dissolved in benzene (15 mL) and to this solution was added tetrabutylammonium iodide (332 mg, 0.9 mmol), H_2O (10 mL), and 50% v/v aqueous NaOH (10 mL). This biphasic mixture was stirred vigorously at ambient temperature while a solution of methanesulfonyl chloride (1.47 g, 993 µL, 12.8 mmol) in benzene (15 mL) was added dropwise via syringe. After this addition, the reaction was stirred for 1 h, then partitioned with ethyl acetate (200 mL) and H_2O (100 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* leaving a crude residue that was eluted through a short plug of silica with 4:1 hexanes:ethyl acetate. The resulting brown solid (2.26 g) was recrystallized from methanol to provide 3-iodo-1-(methylsulfonyl)-1*H*-indole (1.44 g, 43% yield, 2 steps) as tan-colored needles. Following the procedure and mole equivalents indicated above for Example 79 the 3-iodo-1-(methylsulfonyl)-1*H*-indole (350 mg, 1.09 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (150 mg, 0.77 mmol) were cross-coupled to obtain 1-(methylsulfonyl)-3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-1*H*-indole (55 mg, 23% yield) as a tan solid after eluting with 4:1 hexanes:ethyl acetate from a silica gel column. This material was then solubilized in ether (10 mL) and precipitated as the off-white hydrochloride salt (M.p. 152-154°C) upon treatment with of 1M HCl in diethyl ether (2 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.02 (s, 1H), 7.96 (s, 1H), 7.95 (dd, J=7.5 Hz, 1.1 Hz, 1H), 7.81 (dd,

J=7.1 Hz, 1.2 Hz, 1H), 7.49 (ddd, J=7.8 Hz, 7.8 Hz, 1.2 Hz, 1H), 7.43 (ddd, J=7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 3.36 (s, 3H), 2.91 (s, 3H). MS (ESI) 317.0 (M^++H).

Example 88

Synthesis of 2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

2-Chloro-5-iodo-pyridine (3.0g, 12.53 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (2.57 g, 13.16 mmol) were dissolved in DMF (15 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated solution of triphenylphosphine (394 mg, 1.50 mmol), *bis*-triphenylphosphine palladium dichloride (528 mg, 0.75 mmol), CuI (286 mg, 1.50 mmol), tetrabutylammonium iodide (927 mg, 2.51 mmol), and triethylamine (6.33 g, 8.7 mL, 62.7 mmol) in DMF (60 mL) at 40°C. The reaction was warmed to 50°C, and tetrabutylammonium fluoride (13.8 mmol, 13.8 mL of a 1.0M solution in THF) was added via syringe pump over 1.5 h. The reaction was then cooled to ambient temperature and poured into a separatory funnel containing 1:1 hexanes:ethyl acetate (200 mL) where it was washed with 50% dilute brine (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 0.5% to 1.0% methanol in methylene chloride to afford 2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (2.29 g, 78% yield) as an off-white solid, M.p. 138-139°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (d, J=2.1 Hz, 1H), 7.78 (dd, J=8.3 Hz, 2.3 Hz, 1H), 7.45 (s, 1H), 7.33 (d, J=8.2 Hz, 1H), 2.75 (s, 3H). MS (ESI) 234.9 (M^++H).

Example 89

Synthesis of 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-2-phenylpyridine

Phenylboronic acid (569 mg, 4.26 mmol) and 2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 88 (1.00 g, 4.26 mmol) were dissolved in DME (10 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated solution of triphenylphosphine (112 mg, 0.43 mmol), *bis*-triphenylphosphine palladium dichloride (150 mg, 0.21 mmol), and potassium carbonate (1.18 g, 8.52 mmol) in DME (15 mL) and H_2O (25 mL) at 40°C. The reaction was stirred at reflux for 3 h, then cooled to ambient temperature and poured into a separatory funnel containing ethyl acetate (250 mL). The ethyl acetate layer was washed with saturated $NaHCO_3$ (50 mL), and H_2O (2 x 50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 4:1 hexanes:ethyl acetate to afford 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-2-phenylpyridine (1.00 g, 85% yield) as a pale yellow solid, M.p. 102-103°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (d, J=2.1, 1H), 8.00 (m, 2H), 7.89 (dd, J=8.3 Hz, 2.2 Hz, 1H), 7.73 (d, J=8.3 Hz, 1H), 7.45 (s, 1H), 7.43-7.52 (m, 3H), 2.76 (s, 3H). MS (ESI) 277.0 (M^++H).

Example 90

Synthesis of 2-(4-chlorophenyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

Following the procedure and mole equivalents indicated above for Example 89, 4-chloro phenylboronic acid (74 mg, 0.47 mmol) and 2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 88 (100 mg, 0.43 mmol) were cross-coupled to obtain 2-(4-chlorophenyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (105 mg, 79% yield) as a white solid after eluting with 3:1 hexanes:ethyl acetate from a silica gel column. This material was solubilized in ethanol (10 mL) and acidified with 1M HCl in diethyl ether (4 mL). The pale yellow hydrochloride salt (M.p. 193-194°C) was then obtained upon concentration of this solution *in vacuo* and trituration with diethyl ether (3 x 10 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.86 (s, 1H), 7.98 (d, J=8.5 Hz, 2H), 7.95 (d, J=8.6 Hz, 1H), 7.73 (d, J=8.2 Hz, 1H), 7.47 (s, 1H), 7.47 (d, J=8.4 Hz, 2H), 2.76 (s, 3H). MS (ESI) 311.0 (M^++H).

Example 91

Synthesis of 2-(4-methoxyphenyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

Following the procedure and mole equivalents indicated above for Example 89, 4-methoxy phenylboronic acid (106 mg, 0.70 mmol) and 2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 88 (150 mg, 0.64 mmol) were cross-coupled to obtain 2-(4-methoxyphenyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (156 mg, 80% yield) as a white solid, M.p. 125-126°C, after eluting with 2:1 hexanes:ethyl acetate from a silica gel column. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (d, J=1.6 Hz, 1H), 7.96 (d, J=8.8 Hz, 2H), 7.82 (dd, J=8.3 Hz, 2.2 Hz, 1H), 7.63 (d, J=8.2 Hz, 1H), 7.42 (s, 1H), 6.98 (d, J=8.8 Hz), 3.84 (s, 3H), 2.73 (s, 3H). MS (ESI) 307.0 (M^++H).

Example 92

Synthesis of 2-(3-pyridyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

Following the procedure and mole equivalents indicated above for Example 89, pyridine-3-boronic acid (86 mg, 0.70 mmol) and 2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 88 (150 mg, 0.64 mmol) were cross-coupled to obtain 2-(3-pyridyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (80 mg, 45% yield) as a pale yellow solid after eluting with 1:1 hexanes:ethyl acetate from a silica gel column. This material was then solubilized in diethyl ether (10 mL) and precipitated as the pale pink hydrochloride salt upon treatment with of 1M HCl in diethyl ether (2 mL) and trituration with fresh diethyl ether (3 x 5 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 9.63 (s, 1H), 9.37 (d, J=8.2 Hz, 1H), 8.97 (s, 1H), 8.95 (d, J=5.8 Hz, 1H), 8.21-8.31 (m, 3H), 8.07 (s, 1H), 2.88 (s, 3H). MS (ESI) 278.0 (M^++H).

Example 93

Synthesis of 2-(4-pyridyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

Following the procedure and mole equivalents indicated above for Example 89, pyridine-4-boronic acid (86 mg, 0.70 mmol) and 2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 88 (150 mg, 0.64 mmol) were cross-coupled to obtain 2-(4-pyridyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (30 mg, 17% yield) as an off-white solid after eluting with 2:1 ethyl acetate:hexanes from a silica gel column. This material was then solubilized in ether (10 mL) and precipitated as the pale yellow hydrochloride salt (M.p.>185°C, dec.) upon treatment with of 1M HCl in diethyl ether (2 mL) and trituration with fresh diethyl ether (3 x 5 mL). ^{1}H NMR (CD_3OD, 300 MHz) δ 9.01 (s, 1H), 8.98 (d, J=7.0 Hz, 2H), 8.85 (d, J=6.7 Hz, 2H), 8.40 (d, J=8.2 Hz), 8.22 (dd, J=8.2 Hz, 2.0 Hz, 1H), 7.94 (s, 1H), 2.88 (s, 3H). MS (ESI) 278.0 (M^++H).

Example 94

Synthesis of 3-chloro-6-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridazine

3,6-Dichloropyridazine (299 mg, 2.00 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (391 mg, 2.00 mmol) were dissolved in DMF (10 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated solution of triphenylphosphine (105 mg, 0.40 mmol), *bis*-triphenylphosphine palladium dichloride (140 mg, 0.20 mmol), CuI (76 mg, 0.40 mmol), tetrabutylammonium iodide (369 mg, 1.00 mmol), and triethylamine (1.01 g, 1.39 mL, 10.0 mmol) in DMF (15 mL) at 40°C. The reaction was warmed to 50°C, and tetrabutylammonium fluoride (2.10 mmol, 2.10 mL of a 1.0M solution in THF) was added via syringe pump over 1.5 h. The reaction was then cooled to ambient temperature and poured into a separatory funnel containing 1:1 hexanes:ethyl acetate (200 mL) where it was washed with 50% dilute brine (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1.5:1 hexanes:ethyl acetate, then recrystallized from 2:1 ethyl acetate:hexanes to afford 3-chloro-6-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridazine (182 mg, 39% yield) as pale pink needle crystals, M.p. 197-198°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64 (d, J=8.8 Hz, 1H), 7.63 (s, 1H), 7.52 (d, J=8.8 Hz, 1H), 2.77 (s, 3H). MS (ESI) 235.9 (M^++H).

Example 95

Synthesis of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-6-phenylpyridazine

Phenylboronic acid (47 mg, 0.38 mmol) and 3-chloro-6-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridazine from Example 94 (75 mg, 0.32 mmol) were dissolved in DME (2 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated solution of triphenylphosphine (8.4 mg, 0.032 mmol), *bis*-triphenylphosphine palladium dichloride (11.2 mg, 0.016 mmol), and potassium carbonate (89 mg, 0.64 mmol) in DME (2 mL) and H_2O (4 mL) at 40°C. The reaction was stirred at reflux for 16 h, then cooled to ambient temperature

and poured into a separatory funnel containing ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated $NaHCO_3$ (50 mL), and H_2O (2 x 50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1:1 hexanes:ethyl acetate to afford 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-6-phenylpyridazine (43 mg, 49% yield) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (m, 2H), 7.86 (d, J=8.8 Hz, 1H), 7.72 (d, J=8.8 Hz, 1H), 7.62 (s, 1H), 7.51-7.56 (m, 3H), 2.78 (s, 3H). MS (ESI) 278.0 (M^++H).

Example 96

Synthesis of 4-[(6-phenyl-3-pyridinyl)ethynyl]-1,3-thiazol-2-amine

Phenylboronic acid (566 mg, 4.4.64 mmol) and 2,5-dibromopyridine (1.00 g, 4.22 mmol) were dissolved in DME (10 mL) and deoxygenated via argon bubbling for 20 min. This solution was then added via syringe to a deoxygenated solution of triphenylphosphine (111 mg, 0.42 mmol), *bis*-triphenylphosphine palladium dichloride (148 mg, 0.21 mmol), and potassium carbonate (1.17 g, 8.44 mmol) in DME (15 mL) and H_2O (25 mL) at 40°C. The reaction was stirred at reflux for 1 h, then cooled to ambient temperature and poured into a separatory funnel containing ethyl acetate (250 mL). The ethyl acetate layer was washed with saturated $NaHCO_3$ (50 mL), and H_2O (2 x 50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 14:1 hexanes:ethyl acetate to afford 5-bromo-2-phenylpyridine (783 mg, 78% yield) as a white crystalline solid.

5-Bromo-2-phenylpyridine (300 mg, 1.28 mmol) and 4-[(trimethylsilyl)ethynyl]-1,3-thiazol-2-ylamine from Example 78 (210 mg, 1.07 mmol) were added as solids to a deoxygenated solution of triphenylphosphine (56 mg, 0.21 mmol), *bis*-triphenylphosphine palladium dichloride (75 mg, 0.11 mmol), CuI (41 mg, 0.21 mmol), tetrabutylammonium iodide (198 mg, 0.54 mmol), and triethylamine (540 mg, 740 µL, 5.4 mmol) in DMF (15 mL) at 40°C. The reaction was warmed to 60°C, and tetrabutylammonium fluoride (1.17 mmol, 1.17 mL of a 1.0M solution in THF) was added slowly over 1 h. The reaction was then cooled to ambient temperature and poured into a separatory funnel containing 1:1 hexanes:ethyl acetate (250 mL) where it was washed with 50% dilute brine (3 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1:1 hexanes:ethyl acetate to afford 4-[(6-phenyl-3-pyridinyl)ethynyl]-1,3-thiazol-2-amine (186 mg, 63% yield) as a pale yellow solid, M.p. 194-195°C. ^1H NMR (CD_3OD, 300 MHz) δ 8.74 (s, 1H), 7.91-7.96 (m, 3H), 7.78 (d, J=8.3 Hz, 1H), 7.45-7.54 (m, 3H), 6.84 (s, 1H). MS (ESI) 278.0 (M^++H).

Example 97

Synthesis of 3, 4 dihydro-1-naphthalenyl trifluoromethanesulfonate

To a stirred solution of α-tetralone (1.00g, 6.84 mmol) in CH_2Cl_2 (70mL) under argon at ambient temperature was added lutidine (1.20mL, 6.84 mmol) followed by dropwise addition of trifluoromethanesulfonic anhydride (1.73mL, 10.3 mmol). The reaction mixture was stirred for 1h and then concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 10:1 hexane:ethyl acetate to afford 3, 4 dihydro-1-naphthalenyl trifluoromethanesulfonate (1.64g, 87% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36-7.32 (m, 1H), 7.29-7.24 (m, 2H), 7.20-7.16 (m, 1H), 6.03-6.00 (m, 1H), 2.90-2.85 (m, 2H), 2.55-2.48 (m, 2H).

Example 98

Synthesis of 2-(3,4-dihydro-1-naphthalenyl)ethynylpyridine hydrochloride

A stirred suspension of CuI (159 mg, 0.834 mmol), triphenylphosphine (219 mg, 0.834 mmol), $PdCl_2(PPh_3)_2$ (293 mg, 0.417 mmol), and triethylamine (2.90mL, 20.8 mmol) in DME (30mL), was degassed with a stream of argon for several min. A solution of 2-ethynyl pyridine (1.30g, 12.5 mmol) and 3, 4 dihydro-1-naphthalenyl trifluoromethanesulfonate from Example 97 (1.15g, 4.17 mmol) in DME (10mL) was added to the mixture. The mixture was heated to 80°C for 1.5 h. The reaction mixture was cooled to ambient temperature and filtered through a pad of Celite™. The filtrate was concentrated *in vacuo* and the crude material was purified by flash chromatography on silica gel eluting with 8:1 then 5:1 hexane:ethyl acetate to afford 2-(3,4-dihydro-1-naphthalenyl)ethynylpyridine (798mg, 72% yield) as a pale yellow oil.

2-(3,4-Dihydro-1-naphthalenyl)ethynylpyridine (300mg, 1.29 mmol) was dissolved in diethyl ether and treated with HCl in diethyl ether (2.00 mL of a 1 M solution, 2.00 mmol). Upon addition of the HCl solution a white solid precipitated from the solution. The mixture was concentrated *in vacuo* the pale yellow solid was recrystallized from Methanol/diethyl ether. The mother liquor was decanted and the resulting pale yellow solid was dried under high vacuum to afford 2-(3,4-dihydro-1-naphthalenyl)ethynylpyridine hydrochloride (205mg, 18% yield) as a pale yellow solid, M.p. 153-155°C. ^{1}H NMR (CD_3OD, 300MHz) δ 8.76-8.74 (m, 1H), 8.43-8.38 (m, 1H), 8.08-8.05 (d, J=8 Hz, 1H), 7.88-7.83 (m, 1H), 7.66-7.63 (d, J=8.3 Hz, 1H), 7.31-7.18 (m, 3H), 6.91-6.88 (m, 1H), 2.88-2.82 (m, 2H), 2.54-2.47 (m, 2H). MS 232 (M^+H).

Example 99

Synthesis of 5-bromo-N-methoxy-N-methylnicotinamide

To a stirred solution of 5-bromonicotinic acid (2.5g, 12.4 mmol) in CH_2Cl_2 (100mL) was added N, O-dimethylhydroxylamine hydrochloride (1.44g, 14.8mmol), HOBT (1.84g, 13.6mmol), and EDC (2.61g, 13.6 mmol) sequentially as solids followed by diisopropylethylamine (6.46mL, 37.1mmol).

The mixture was stirred at ambient temperature under argon for 1 h. The reaction mixture was concentrated *in vacuo* and redissolved in ethyl acetate. The organic material was washed with 1M HCl and brine (3 x 25mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to afford 5-bromo-N-methoxy-N-methylnicotinamide (2.99g, 51% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 300MHz) δ 8.21-8.20 (m, 1H), 7.85-7.82 (m, 1H), 7.73-7.70 (m, 1H), 3.58 (s, 3H), 3.40 (s, 3H).

Example 100

Synthesis of N-methoxy-N-methyl-5-[(2-methyl-1, 3-thiazol-4-yl)ethynyl] nicotinamide

A stirred suspension of CuI (257 mg, 1.35 mmol), triphenylphosphine (354 mg, 1.35 mmol), $PdCl_2(PPh_3)_2$ (467 mg, 0.665 mmol), tetrabutylammonium iodide (1.89g, 5.12 mmol) and triethylamine (3.57 mL, 25.6 mmol) in DMF (50mL), was degassed with a stream of argon for several minutes and warmed to 40°C. 2-Methyl-4[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (1.00g, 5.12 mmol) and 5-bromo-N-methoxy-N-methylnicotinamide from Example 99 (1.63 g, 6.65 mmol) was added to the reaction mixture. The mixture was heated to 70°C and TBAF in THF (6.65 mL, 1.0 M solution, 6.65 mmol) was added via syringe pump over 2 h. The reaction mixture was cooled to ambient temperature and diluted with 1:1 hexane:ethyl acetate. The organic material was washed with dilute brine (3 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (2:1 then 1:1 hexane:ethyl acetate) to afford N-methoxy-N-methyl-5-[(2-methyl-1, 3-thiazol-4-yl)ethynyl] nicotinamide (708 mg, 48% yield) as an orange oil. ^1H NMR ($CDCl_3$, 300MHz) δ 8.89-8.84 (m, 2H), 8.19-8.17 (m, 1H), 7.55-7.53 (m, 1H), 3.57 (s, 3H), 3.40 (s, 3H), 2.74 (s, 3H). MS 288 (M^+H).

Example 101

Synthesis of (4-fluorophenyl){5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-pyridinyl}methanone

To a stirred solution of N-methoxy-N-methyl-5-[(2-methyl-1, 3-thiazol-4-yl)ethynyl] nicotinamide from Example 100 (50 mg, 0.174 mmol) at ambient temperature under argon was added a solution 4-fluorophenylmagnesium bromide in THF (0.696 mL, 1.0M solution, 0.696 mmol). The reaction mixture was stirred for 24 h and then diluted with H_2O. The aqueous solution was extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with brine (2 x 25mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 3:1 then 2:1 hexane:ethyl acetate to afford (4-fluorophenyl){5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-pyridinyl}methanone (15 mg, 27% yield) as a pale yellow solid, M.p. 132-134°C. ^1H NMR ($CDCl_3$, 300MHz) δ 9.02-8.95 (m, 2H), 8.20-8.19 (m, 1H), 7.89-7.85 (m, 2H), 7.48 (s, 1H), 7.25-7.19 (m, 2H), 2.76 (s, 3H). MS 323 (M^+H).

Example 102

Synthesis of (4-methoxyphenyl){5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-pyridinyl}methanone

To a stirred solution of N-methoxy-N-methyl-5-[(2-methyl-1, 3-thiazol-4-yl)ethynyl] nicotinamide from Example 100 (50 mg, 0.174 mmol) at ambient temperature under argon was added a solution 4-anisylmagnesium bromide in THF (1.39mL, 0.5M solution, 0.696 mmol). The reaction mixture was stirred for 24 h and then diluted with H_2O. The aqueous solution was extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with brine (2 x 25mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 3:1 then 2:1 hexane:ethyl acetate to afford (4-methoxyphenyl){5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-pyridinyl}methanone (13 mg, 22% yield) as a pale yellow solid, M.p. 97-99°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.94-8.90 (m, 2H), 8.18-8.17 (m, 1H), 7.85-7.82 (m, 2H), 7.47 (s, 1H), 7.02-6.99 (m, 2H), 3.92 (s, 3H), 2.76 (s, 3H). MS 335 (M^+H).

Example 103

Synthesis of 2-(2-cyclopropylethynyl)thiazole

2-Bromo-1,3-thiazole (1.31 g, 8.0 mmol), CuI (143 mg, 0.75 mmol), $PdCl_2$ (45 mg, 0.75 mmol), PPh_3 (197 mg, 0.75 mmol), and K_2CO_3 (4.5 g, 33 mmol) were combined in DME (50 mL) and H_2O (25 mL), and argon gas was bubbled through the suspension for several min to deoxygenate the mixture. Cyclopropyl trimethylsilylacetylene (1.8 g, 13.3 mmol) was added and the reaction was heated at reflux for 12 h. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with H_2O (200 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. This material was purified by column chromatography eluting with 4:1 hexane:ethyl acetate to afford 2-(2-cyclopropylethynyl)thiazole (800 mg, 67%) as a light brown oil.

p-Toluenesulfonic acid (1.02 g, 5.4 mmol) and 2-(2-cyclopropylethynyl)thiazole (800 mg, 5.3 mmol) were dissolved in Methanol (50 mL), and the solution was concentrated *in vacuo*. The resulting black viscous oil was triturated with diethylether with sonication. The diethylether layer was decanted and the remaining brown gum was dried *in vacuo*. Material was free based with aqueous K_2CO_3, and extracted with ethyl acetate (2 x 75 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 4:1 hexane:ethyl acetate to afford 2-(2-cyclopropylethynyl)thiazole (150 mg, 19%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, J= 3 Hz, 1H), 7.25 (d, J= 3 Hz, 1H), 1.50 (m, 1H), 0.93 (m, 4H). MS (API-ES Positive) 150 (M+H).

Example 104

Synthesis of 3-(2-pyridinylethynyl)-2-cyclohexen-1-one

A solution of 2-ethynylpyridine (10.3 g, 100 mmol) in THF (200 mL) was cooled to -50°C and a solution of *n*-BuLi (100 mmol, 2.0 M in hexane) was added slowly keeping the solution temperature below -40° C. After 30 min at reduced temperature the solution became opaque, brown and slightly viscous. 3-Ethoxy-2-cyclohexen-1-one (15.4 g, 110 mmol) was added all at once and the solution was allowed to warm slowly to ambient temperature with stirring. After 12 h the dark solution was acidified with HCl (400 mmol, 2.0 M), followed after 30 min by basification with solid K_2CO_3. The mixture was partitioned between ethyl acetate and H_2O, the H_2O layer was washed with a further portion of ethyl acetate, the combined organic layers were washed with H_2O (200 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 2:1 to 1:1 hexane:ethyl acetate to afford a yellow oil (10.5 g, 53%). This material was crystallized from ethyl acetate to afford two crops of light yellow flakes (5.9 g, 30%) M.P, 74-75° C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (m, 1H), 7.72 (m, 1H), 7.51 (m, 1H), 7.30 (m, 1H), 6.37 (m, 1H), 2.59 (m, 2H), 2.46 (m, 2H), 2.09 (m, 2H). MS (ESI) 197 (M+).

Example 105

Synthesis of 3-(2-pyridinylethynyl)-2-cyclohexen-1-one oxime

Hydroxylamine hydrochloride (350 mg, 5.0 mmol) and KOH (560 mg, 10 mmol) were dissolved in wet ethanol (15 mL). 3-(2-Pyridinylethynyl)-2-cyclohexen-1-one from Example 104 (0.5 g, 2.5 mmol) was added and the mixture heated at reflux for 2 h. The solution was allowed to cool and the solids filtered. The ethanol soluble portion was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to afford 3-(2-pyridinylethynyl)-2-cyclohexen-1-one oxime (375 mg, 70 %) as a tan solid. M.p. 125-127°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (m, 1H), 7.68 (m, 1H), 7.47 (m, 1H), 7.24 (m, 1H), 6.75 (s, 1H), 2.65 (m, 2H), 2.41 (m, 2H), 1.84 (m, 2H). MS (API-ES positive) 213 (M+H).

Example 106

Synthesis of (E, Z)-3-(2-pyridinylethynyl)-2-cyclohexene-1-one O-methyloxime

To a solution of 3-(2-pyridinylethynyl)-2-cyclohexene-1-one from Example 104 (10 mg, 0.05 mmol) in ethanol (0.3 mL) was added methoxylamine hydrochloride (30-35 wt. % in H_2O; 7μl, 0.05 mmol) in a 10 ml Teflon reaction tube. Piperidinomethyl polystyrene (28 mg of 3.63 mmol/g beads, 0.1 mmol) was added and the resulting suspension was heated at 80°C in an orbital shaker. After shaking at 80°C for 16 h, the reaction was cooled to ambient temperature and chloroformate polystyrene (47.5 mg of 1.0 mmol/g beads, 0.05 mmol) was added. The reaction was allowed to shake at 40°C for 1 hour, then cooled to ambient temperature, and tris (2-aminoethyl)amine polystyrene (11 mg of 4.5 mmol/g beads, 0.05 mmol) was added. The reaction was then allowed to shake at 40°C for 1 hour, then cooled,

and diethyl ether (0.3 ml) was added. The reaction was vortexed and filtered using a fritted syringe attached to a vacuum block. The collected sample was then concentrated *in vacuo* using a Savant rotary evaporator to afford 3-(2-pyridinylethynyl)-2-cyclohexene-1-one O-methyloxime as a mixture of *E, Z,* isomers (12 mg, 90% yield) as a light brown oil. 1 H NMR (CDCl3, 300 MHz) δ 8.61-8.59 (m, 1H), 7.68-7.67 (m, 1H), 7.47-7.44 (m, 1H), 7.28-7.23 (m, 1H), 7.17-6.57 (m, 1H), 3.90 (d J=10.9 Hz, 1H), 2.57-2.52 (m, 2H), 2.47-2.39 (m, 2H), 1.91-1.88 (m, 2H), 1.83-1.79 (m, 2H); MS (ESI) 226.28 (M^++H).

Example 107

Synthesis of (E, Z)-3-(2-pyridinylethynyl)-2-cyclohexen-1-one O-ethyloxime

To a solution of 3-(2-pyridinylethynyl)-2-cyclohexene-1-one from Example 104 (20 mg, 0.10 mmol) in ethanol (0.6 mL) was added O-ethylhydroxylamine hydrochloride (10 mg, 0.10 mmol) in a 10 ml Teflon reaction tube. Piperidinomethyl polystyrene (56mg of 3.63 mmol/g beads, 0.2 mmol) was added and the resulting suspension was heated at 80°C in an orbital shaker. After shaking at 80°C for 16 h, the reaction was cooled to ambient temperature and chloroformate polystyrene (95 mg of 1.0 mmol/g beads, 0.10 mmol) was added. The reaction was allowed to shake at 40°C for 1 hour, cooled to ambient temperature, and treated with tris (2-aminoethyl)amine polystyrene (22 mg of 4.5 mmol/g beads, 0.10 mmol). The reaction was then allowed to shake at 40°C for 1 hour, then cooled, and diethyl ether (0.6 ml) was added. The reaction was vortexed and filtered using a fritted syringe attached to a vacuum block. The collected sample was then concentrated *in vacuo* using a Savant rotary evaporator to afford 3-(2-pyridinylethynyl)-2-cyclohexen-1-one O-ethyloxime as a mixture of *E, Z* isomers (22 mg, 91% yield) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61-8.59 (m, 1H), 7.70-7.63 (m, 1H), 7.47-7.43 (m, 1H), 7.28-7.23 (m, 1H), 7.22-6.58 (m, 1H), 4.20-4.10 (m, 2H), 2.56 (t J=6.6 Hz, 2H), 2.47-2.38 (m, 2H), 2.47-2.39 (m, 2H), 1.94-1.87 (m, 2H), 1.85-1.76 (m, 2H), 1.29 (t J=6.0 Hz, 3H); MS (ESI) 240.30 (M^++H).

Example 108

Synthesis of E/Z-3-(2-pyridinylethynyl)-2-cyclohexen-1-one O-allyloxime

To a solution of 3-(2-pyridinylethynyl)-2-cyclohexen-1-one from Example 104 (513 mg, 2.60 mmol) in ethanol (15 mL) was added O-allylhydroxylamine hydrochloride (393 mg, 3.59 mmol). Piperidinomethyl polystyrene (1.54 g of 3.63 mmol/g beads, 5.6 mmol) was added and the resulting suspension was heated in an oil bath at 80°C. After stirring at 80°C for 16 h, TLC analysis showed no starting 3-(2-pyridinylethynyl)-2-cyclohexen-1-one remaining. The reaction mixture was cooled, diluted with ether, and filtered through a glass frit to remove the resin. The filtrate was concentrated to afford a yellow oil which was purified by column chromatography eluting with hexane, 20:1, 9:1, then

8.5:1.5 hexane:ethyl acetate to afford E,Z-3-(2-pyridinylethynyl)-2-cyclohexen-1-one *O*-allyloxime (550 mg, 83% yield) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63-8.60 (m, 1H), 7.70-7.64 (m, 1H), 7.48-7.44 (m, 1H), 7.28-7.22 (m, 1H), 6.60-6.59 (m, 1H), 6.07-5.96 (m, 1H), 5.36-5.22 (m, 2H), 4.64-4.59 (m, 2H), 2.62-2.58 (m, 1H), 2.49-2.40 (m, 2H), 1.95-1.78 (m, 2H); MS (ESI) 253.1 (M^++H).

Example 109

Synthesis of (Z)-methyl-[3-(2-pyridinylethynyl)-2-cyclohexen-1-ylidene]ethanoate

Trimethylphosphonoacetate (462 mg, 2.5 mmol) was dissolved in THF (20 mL) and the solution was cooled to 0° C at which time LiHDMS (2.6 mL, 1.0 M in THF) was added slowly. After 30 min 3-(2-pyridinylethynyl)-2-cyclohexen-1-one from Example 104 (0.5 g, 2.5 mmol) was added and the solution was allowed to warm to ambient temperature. After a further 3 h the mixture was partitioned between ethyl acetate and H_2O, the aqueous layer was washed with a further portion of ethyl acetate, the combined organic layers were washed with H_2O (50 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting on silica gel with 1.5:1 then 1:1 hexane:ethyl acetate to yield methyl-[3-(2-pyridinylethynyl)-2-cyclohexen-1-ylidene]ethanoate as a mixture of E and Z double bond isomers. This mixture was further purified by reverse phase HPLC to obtain a major isomer and a minor isomer. The major isomer was identified as the Z-isomer based on the lack of NOESY correlation between the two vinyl protons. MP 65-68°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (d, J=5 Hz, 1H), 7.98 (m, 1H), 7.67 (m, 1H), 7.47 (m, 1H), 7.23 (m, 1H), 5.57 (s, 1H), 3.73 (s, 3H), 2.44 (m, 3H), 1.84 (m, 3H); MS (API-ES positive) 254 (M+H).

Example 110

Synthesis of 2-{[(3S)-3-methyl-1-cyclopenten-1-yl]ethynyl}pyridine & 2-{[(4S)-4-methyl-1-cyclopenten-1-yl]ethynyl}pyridine

To a solution of 2-ethynylpyridine (0.6 mL, 6.0 mmol) in THF (2 mL) at –40° C was added *n*-butyllithium (3.75 mL, 6.0 mmol). After stirring at reduced temperature for 30 min the solution was added rapidly to a solution of (R)-(+)-3-methylcyclopentanone (0.65 mL, 6.0 mmol) in THF (10 mL). The mixture was allowed to warm to ambient temperature over 16 h, then partitioned between H_2O and ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to afford (R)-(+)-3-methyl-1-(2-pyridinylethynyl)cyclopentanol as a dark oil. This material was dissolved in pyridine/CH_2Cl_2 (10 mL, 1/1), $POCl_3$ (0.55 mL, 6.0 mmol) was added, and the mixture was heated to reflux for 4 h. After cooling, the $POCl_3$ and pyridine were removed *in vacuo*, and the residue was partitioned between H_2O and ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel

eluting with 2:1 hexane:ethyl acetate to afford 2-{[(3*S*)-3-methyl-1-cyclopenten-1-yl]ethynyl}pyridine and 2-{[(4*S*)-4-methyl-1-cyclopenten-1-yl]ethynyl}pyridine (0.425 g, 38%) as a dark brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, J=9 Hz, 1H), 7.63 (m, 1H), 7.42 (m, 1H), 7.20 (m, 1H), 6.17 (m, 1H), 2.90 (m, 0.5H), 2.61 (m, 2H), 2.16 (m, 2H), 1.47 (m, 0.5H), 1.06 (d, J=12 Hz, 3H). GC/MS two peaks 11.88 and 11.91 min. (ESI) 182 (M+).

Example 111

Synthesis of 2-[(3,5-dimethyl-1-cyclohexen-1-yl)ethynyl]pyridine

The procedure was carried out as for Example 110 using 3,5-*cis*-dimethylcyclohexanone (756 mg, 6.0 mmol), to give 2-[(3,5-dimethyl-1-cyclohexen-1-yl)ethynyl]pyridine (0.325 g, 25%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.63 (m, 1H), 7.41 (m, 1H), 7.18 (m, 1H), 6.15 (m, 1H), 2.27 (m, 2H), 1.79 (m, 3H), 1.01 (m, 7H). GC/MS 12.96 min. (ESI) 211 (M+).

Example 112

Synthesis of 2-[(3,4-dimethyl-1-cyclopenten-1-yl)ethynyl]pyridine

The procedure was carried out as for Example 110 using 3,4-dimethylcyclopentanone (672 mg, 6.0 mmol), to yield a mixture of *cis* and *trans* 2-[(3,4-dimethyl-1-cyclopenten-1-yl)ethynyl]pyridine (0.51 g, 43%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.63 (m, 1H), 7.43 (m, 1H), 7.19 (m, 1H), 6.14 (m, 1H), 2.64-2.80 (m, 2H), 2.43 (m, 1H), 2.22 (m, 1H), 1.89 (m, 1H), 1.07 (m, 3H), 0.94 (m, 3H). GC/MS two peaks 12.15 and 112.44 min. (ESI) 196 (M+).

Example 113

Synthesis of -{[5-(trifluoromethyl)-1-cyclohexen-1-yl]ethynyl}pyridine & 2-{[3-(trifluoromethyl)-1-cyclohexen-1-yl]ethynyl}pyridine

The procedure was carried out as for Example 110 using 3-trifluoromethylcyclohexanone (960 mg, 6.0 mmol), to yield a 3:1 mixture of 2-{[5-(trifluoromethyl)-1-cyclohexen-1-yl]ethynyl}pyridine and 2-{[3-(trifluoromethyl)-1-cyclohexen-1-yl]ethynyl}pyridine (0.51 g, 43%) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.65 (m, 1H), 7.43 (m, 1H), 7.21 (m, 1H), 6.32 (m, 0.75H), 6.21 (m, 0.25H), 2.98 (m, 0.25H), 2.25-2.57 (m, 3.5H), 2.01 (m, 2H), 1.58 (m, 1H), 1.29 (m, 0.25H). GC/MS three peaks 12.22, 12.37 and 12.49 min. (ESI) 251 (M+), 252 (M+H).

Example 114

Synthesis of 2-(1,4,4a,5,6,7,8,8a-octahydro-2-naphthalenylethynyl)pyridine and 2-(3,4,4a,5,6,7,8,8a-octahydro-2-naphthalenylethynyl)pyridine

The procedure was carried out as for Example 110 using *cis/trans* 2-decalone (1.83 g, 12 mmol) to yield a mixture of four stereoisomers each of 2-(1,4,4a,5,6,7,8,8a-octahydro-2-naphthalenylethynyl)pyridine & 2-(3,4,4a,5,6,7,8,8a-octahydro-2-naphthalenylethynyl)pyridine (0.50 g, 9%) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, J=5 Hz, 1H), 7.63 (m, 1H), 7.37 (m, 1H),

7.18 (m, 1H), 6.27 (m, 0.5H), 6.20 (m, 0.5H), 2.05-2.34 (m, 3H), 1.79 (m, 3H), 1.48 (m, 7H), 1.00 (m, 1H). MS (API-ES positive) 238 (M+H).

Example 115

Synthesis of 2-[(3-methyl-1-cyclohexen-1-yl)ethynyl]pyridine

A solution of 3-methyl-2-cyclohexen-1-one (990 mg, 9.0 mmol) in THF was chilled to –78° C and L-selectride (9.5 mmol, 1.0 M in THF) was added slowly via syringe. After 1 h at reduced temperature N-phenyltriflimide (3.2 g, 9.0 mmol) was added all at once. The reaction was allowed to warm to ambient temperature while stirring overnight. The reaction was diluted with two volumes of hexane, and the organic phase was washed with H_2O, then 10% aqueous NaOH and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane to afford 3-methyl-1-cyclohexen-1-yl trifluoromethanesulfonate (400 mg, 18%).

3-methyl-1-cyclohexen-1-yl trifluoromethanesulfonate (400 mg, 1.6 mmol), CuI (30 mg, 0.15 mmol), $PdCl_2$ (9 mg, 0.05 mmol), PPh_3 (40 mg, 0.15 mmol), and K_2CO_3 (552 mg, 4.0 mmol) were combined in DME (15 mL) and H_2O (15 mL), and argon gas was bubbled through the suspension for several min to deoxygenate the mixture. 2-Ethynylpyridine (412 mg, 4.0 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h and then heated at reflux for 1 h. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with H_2O (100 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 3:1 hexane:ethyl acetate to afford 2-[(3-methyl-1-cyclohexen-1-yl)ethynyl]pyridine (250 mg, 80%) as a clear oil containing 5% of a regioisomer. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (m, 1H), 7.62 (m, 1H), 7.40 (m, 1H), 7.18 (m, 1H), 6.18 (m, 1H), 2.31 (m, 1H), 2.21 (m, 2H), 1.79 (m, 2H), 1.55 (m, 1H), 1.18 (m, 1H), 1.02 (d, J=7 Hz, 3H). MS (API-ES positive) 198 (M+H).

Example 116

Synthesis of 5-methyl-1-cyclohexen-1-yl trifluoromethanesulfonate

To a solution of 5-methyl-1,3-cyclohexanedione (1.0 g, 7.9 mmol) in ethanol (25 mL) was added *p*-toluenesulfonic acid (85 mg, 0.5 mmol), and the reaction was heated to 60° C for 16 h. The reaction was cooled and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica eluting with hexane to give 3-ethoxy-5-methyl-2-cyclohexen-1-one (1.2 g, quantitative yield) as a clear oil.

3-Ethoxy-5-methyl-2-cyclohexen-1-one (1.2 g, 7.8 mmol) was dissolved in THF (25 mL). $LiAlH_4$ (3.5 mmol, 1.0M in THF) was added, and the reaction was allowed to stir at ambient temperature for 3 h. H_2SO_4 (10% aqueous, 25 mL) was added slowly and the mixture was partitioned

between H_2O and ethyl acetate. The organics were concentrated *in vacuo* to give 5-methyl-2-cyclohexen-1-one (715 mg, 83%) as a clear oil.

A solution of 5-methyl-2-cyclohexen-1-one (715 mg, 6.5 mmol) in THF was chilled to -78° C and L-selectride (6.0 mmol, 1.0 M in THF) was added slowly *via* syringe. After 1 h at reduced temperature N-phenyltriflimide (1.8 g, 5.0 mmol) was added all at once. The reaction was allowed to warm to ambient temperature while stirring overnight. The reaction was diluted with two volumes of hexane, and the organics were washed with H_2O, then 10% aqueous NaOH and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane to afford 5-methyl-1-cyclohexen-1-yl trifluoromethanesulfonate (450 mg, 28%). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.74 (m, 1H), 2.34 (m, 1H), 2.20 (m, 2H), 2.02 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H), 1.23 (m, 1H), 1.03 (d, J=6.5 Hz, 3H). MS (EI ionization) 244 (M+).

Example 117

Synthesis of 2-[(5-methyl-1-cyclohexen-1-yl)ethynyl]pyridine

5-Methyl-1-cyclohexen-1-yl trifluoromethanesulfonate (450 mg, 1.8 mmol), CuI (57 mg, 0.3 mmol), $PdCl_2$ (18 mg, 0.1 mmol), PPh_3 (79 mg, 0.3 mmol), and K_2CO_3 (640 mg, 4.7 mmol) were combined in DME (20 mL) and H_2O (20 mL), and argon gas was bubbled through the suspension for several min to deoxygenate the mixture. 2-Ethynylpyridine (484 mg, 4.7 mmol) was added and the reaction stirred at ambient temperature for 16 h, then heated at reflux for 1 h. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with H_2O (100 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 3:1 hexane:ethyl acetate to afford 2-[(5-methyl-1-cyclohexen-1-yl)ethynyl]pyridine (290 mg, 82%) as a light yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.56 (m, 1H), 7.62 (m, 1H), 7.40 (m, 1H), 7.17 (m, 1H), 6.31 (m, 1H), 2.33 (m, 1H), 2.20 (m, 2H), 1.89 (m, 1H), 1.71 (m, 2H), 1.22 (m, 1H), 0.99 (d, J= 6.5 Hz, 3H).

Example 118

Synthesis of 3-(2-pyridinylethynyl)-2-cyclohexen-1-ol

3-(2-Pyridinylethynyl)-2-cyclohexen-1-one from Example 104 (294 mg, 1.5 mmol) and $CeCl_3$ heptahydrate (381 mg, 1.0 mmol) were dissolved in CH_3OH (16 mL). $NaBH_4$ (127 mg, 3.4 mmol) was added portionwise over 5 min. After 15 min. the reaction was quenched with H_2O and partitioned between H_2O and ethyl acetate. The organics were washed with aq. NH_4Cl, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 1:1 hexane:ethyl acetate to afford a clear oil (275 mg, 92%).

p-Toluenesulfonic acid (263 mg, 1.4 mmol) and 3-(2-pyridinylethynyl)-2-cyclohexen-1-ol (275 mg, 1.4 mmol) were dissolved in ethanol:Methanol (1:1, 40 mL), and the solution was concentrated *in vacuo*. The resulting viscous oil was triturated with diethylether and sonicated. The diethylether layer was decanted and remaining oil was dried *in vacuo*. This material was free based with aqueous K_2CO_3, and extracted with ethyl acetate (2 x 35 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography silica gel eluting with 3:2 hexane:ethyl acetate to afford 3-(2-pyridinylethynyl)-2-cyclohexen-1-ol (160 mg, 57%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.65 (m, 1H), 7.42 (m, 1H), 7.22 (m, 1H), 6.33 (m, 1H), 4.32 (m, 1H), 2.25 (m, 2H), 2.13 (m, 1H), 1.87 (br m, 2H), 1.63 (m, 2H). MS (API-ES Positive) 199 (M+).

Example 119

Synthesis of 4, 6-dimethyl-2-pyrimidinyl trifluoromethanesulfonate

To a stirred solution of 4,6-dimethyl-2-hydroxypyrimidine (5.0 g, 40 mmol) in anhydrous CH_2Cl_2 (100 mL) was added triethylamine (11.2 mL, 80 mmol), followed by slow addition of trifluoromethanesulfonic anhydride (6.8 mL, 40 mmol) at 0°C under argon. The reaction mixture was allowed to warm to 22°C and stirred overnight. The reaction mixture was then diluted with CH_2Cl_2 (100 mL). The organic phase was washed with sat. NaCl (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a dark oil. Purification by flash chromatography on silica gel eluting with 3:1 hexane:ethyl acetate afforded 4, 6-dimethyl-2-pyrimidinyl trifluoromethanesulfonate as a brown oil (6.0 g, 58%). ^{1}H NMR ($CDCl_3$) δ: 7.10 (s, 1 H), 2.45 (s, 6 H).

Example 120

Synthesis of 4,6-dimethyl-2-(phenylethynyl)pyrimidine hydrochloride

A stirred solution of 4, 6-dimethyl-2-pyrimidinyl trifluoromethanesulfonate from Example 119 (5.0 g, 19.5 mmol) in 2:1 DME:H_2O (100 mL) was degassed with argon for 10 min. Then K_2CO_3 (6.7 g, 48.8 mmol), CuI (0.37 g, 1.95 mmol), $PdCl_2(Ph_3P)_2$ (0.68 g, 0.98 mmol) and phenylacetylene (5.4 mL, 48.8 mmol) were added at 22°C. The resulting mixture was then heated at 90°C for 2 h under argon. The reaction mixture was then cooled to 22°C and filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure to give, after purification by flash chromatography on silica gel eluting with 3:1 hexane:ethyl acetate, the desired compound as a brown crystal which was subsequently treated with a solution of 1M HCl in diethyl ether (20 mL) to yield 4,6-dimethyl-2-(phenylethynyl)pyrimidine hydrochloride as a yellow solid (3.0 g, 55%). M.P 149-150°C. ^{1}H NMR (CD_3OD) δ: 7.76-7.73 (m, 2 H), 7.67 (s, 1 H), 7.60-7.49 (m, 3 H), 2.69 (s, 3 H) ppm; MS(ES): 209 $(M+H)^+$.

Example 121

Synthesis of 3-(6-methyl-2-pyridinyl)2-propyn-1-ol

A solution of 2-bromo-6-methylpyridine (2.5 g, 14.5 mmol) in 2:1 DME:H_2O (30 mL) was degassed with argon for 10 min. Then $PdCl_2(Ph_3P)_2$ (1.0 g, 1.4 mmol), CuI (0.8 g, 4.3 mmol), K_2CO_3 (5.0 g, 36.3 mmol) were added followed by propargyl alcohol (2.1 mL, 36.3 mmol). The resulting mixture was heated at 90°C under argon for 2 h, allowed to cool to 22°C, then filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with 2:1 ethyl acetate:hexane to give the cross-coupled product 3-(6-methyl-2-pyridinyl)2-propyn-1-ol as a yellow solid (1.0 g, 47%). ^{1}H NMR ($CDCl_3$) δ: 7.58-7.53 (m, 1 H), 7.27-7.25 (d, J = 7.5 Hz, 1 H), 7.13-7.10 (d, J = 7.8 Hz, 1 H), 4.54 (s, 2 H), 2.55 (s, 3 H).

Example 122

Synthesis of 3-(6-methyl-2-pyridinyl)-2-propynyl methanesulfonate

To a stirred solution of 3-(6-methyl-2-pyridinyl)2-propyn-1-ol from Example 121 (1.0 g, 6.8 mmol) in anhydrous CH_2Cl_2 (20 mL) was added triethylamine (1.0 mL, 7.5 mmol) followed by methanesulfonyl chloride (0.6 mL, 7.5 mmol) at 0°C under argon. After 2 h the reaction mixture was diluted with CH_2Cl_2 (50 mL), the organic phase was washed with sat. $NaHCO_3$ (3 x 10 mL) and sat. NaCl (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 3-(6-methyl-2-pyridinyl)-2-propynyl methanesulfonate as a brown oil (1.4 g, 89%) that was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ: 7.68-7.62 (m, 1 H), 7.28 (d, J = 7.5 Hz, 1 H), 7.15 (d, J = 7.8 Hz, 1 H), 4.55 (s, 2 H), 3.09 (s, 3 H), 2.57 (s, 3 H).

Example 123

Synthesis of 2-methyl-6-(3-phenyl-1-propynyl)pyridine

To a stirred solution of 3-(6-methyl-2-pyridinyl)-2-propynyl methanesulfonate from Example 122 (1.2 g, 5.3 mmol) in anhydrous THF (10 mL) under argon at 0°C was added phenylmagnesium bromide (2.1 mL, 6.4 mmol). The reaction mixture was then warmed to 22°C, stirred for 1 h then diluted with ethyl acetate (50 mL). The organic phase was washed with sat. $NaHCO_3$ (3 x 10mL), H_2O (3 x 10 mL) and sat. NaCl (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a dark oil. Purification by flash chromatography on silica gel eluting with 4:1 hexane:ethyl acetate to afford 2-methyl-6-(3-phenyl-1-propynyl)pyridine as a brown oil (360 mg, 33%). ^{1}H NMR ($CDCl_3$) δ: 7.54-7.50 (m, 1 H), 7.37-7.19 (m, 5 H), 7.09-7.06 (d, J = 7.8 Hz, 1 H), 6.93-6.90 (d, J = 7.5 Hz, 1 H), 3.79 (s, 2H), 2.55 (s, 3H).

Example 124

Synthesis of 2-methyl-6-(3-phenyl-1,2-propadienyl)pyridine

To a stirred solution of 2-methyl-6-(3-phenyl-1-propynyl)pyridine from Example 123 (100 mg, 0.48 mmol) in anhydrous THF (10 mL) at -78°C under argon was slowly added n-BuLi (2.5 M in hexane, 0.23 mL, 0.58 mmol). The resulting reddish reaction mixture was stirred for 30 min, then quenched with Methanol (1 mL). The reaction mixture was then warmed to 22°C and taken up in ethyl acetate (50 mL). The organic phase was washed with H_2O (3 x 15 mL) and sat. NaCl (3 x 15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 6:1 hexane:ethyl acetate afforded 2-methyl-6-(3-phenyl-1,2-propadienyl)pyridine as a yellow oil (40 mg, 40%). MS(ES): 208 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 7.51-7.45 (m, 1 H), 7.39-7.21 (m, 6 H), 6.99-6.96 (d, J = 7.5 Hz, 1 H), 6.77-6.75 (d, J = 6.6 Hz,1 H), 6.65-6.62 (d, J = 6.6 Hz, 1 H), 2.55 (s, 3 H).

Example 125

Synthesis of methyl 2-{[(trifluoromethyl)sulfonyl]oxy}-1-cyclopentene-1-carboxylate

To a stirred solution of methyl 2-oxocyclopentane carboxylate (5.0 g, 35.2 mmol) in anhydrous CH_2Cl_2 under argon at 0°C (40 mL) was added NaH (60 % in oil, 1.4 g, 35.2 mmol). After stirring for 10 min the resulting yellow cloudy suspension was treated with trifluoromethanesulfonic anhydride (7.1mL, 42.2 mmol). The reaction mixture was then warmed to 22°C and after 2 h the reaction was treated with 10% HCl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL), the combined organic extracts were washed with sat. NaCl (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel eluting with 20:1 hexane:ethyl acetate to afford methyl 2-{[(trifluoromethyl)sulfonyl]oxy}-1-cyclopentene-1-carboxylate as a colorless oil (6.5 g, 67%). ^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 3 H), 2.78-2.69 (m, 4 H), 2.00-2.00 (m, 2 H).

Example 126

Synthesis of methyl 2-(2-pyridinylethynyl)-1-cyclopentene-1-carboxylate

A solution of methyl 2-{[(trifluoromethyl)sulfonyl]oxy}-1-cyclopentene-1-carboxylate from Example 125 (2.0 g, 7.2 mmol) in DMF at 22°C was degassed with argon for 10 min. Triethylamine (2.5 mL, 18 mmol), CuI (0.41 g, 2.2 mmol), $PdCl_2(Ph_3P)_2$ (0.5 g, 0.72 mmol), n-Bu_4NI (8.0 g, 21.6 mmol) and 2-ethynylpyridine (1.9 g, 18.0 mmol) were added at 22°C and the resulting mixture was heated at 90°C for 2 h under argon. The reaction mixture was allowed to cool to 22°C and filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure to give, after purification by flash chromatography on silica gel eluting with 4:1 hexane:ethyl acetate, methyl 2-(2-pyridinylethynyl)-1-cyclopentene-1-carboxylate as a brown solid (1.2 g, 72 %). M.P. 45-46°C.

MS(ES): 228 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 8.63-8.61 (m, 1 H), 7.68-7.65 (m, 1 H), 7.55-7.53 (m, 1 H), 7.26-7.23 (m, 1 H), 3.81 (s, 3 H), 2.81-2.75 (m, 4 H), 2.01-1.90 (m, 2 H).

Example 127

Synthesis of 2-(2-pyridinylethylnyl)-1-cyclopentene-1-carboxylic acid

To a solution of methyl 2-(2-pyridinylethynyl)-1-cyclopentene-1-carboxylate from Example 126 (1.0 g, 4.4 mol) in 3:1 Methanol:H_2O (20 ml) was added LiOH.H_2O (0.55 g, 13.2 mmol). After stirring at 22°C for 5 h the reaction mixture was treated with 10% HCl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic extracts were washed with sat. NaCl (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude solid. Purification by flash chromatography on silica gel eluting with 10:1 CH_2Cl_2:CH_3OH afforded 2-(2-pyridinylethylnyl)-1-cyclopentene-1-carboxylic acid as a gray solid (330 mg, 35%). M.P. 151-152°C. MS(ES): 214 (M+H)+, ^{1}H NMR (CD_3OD) δ: 8.53-8.50 (m, 1 H), 7.88-7.82 (m 1 H), 7.62-7.59 (m, 1 H), 7.43-7.38 (m, 1 H), 2.81-2.72 (m, 4 H), 2.06-1.96 (m, 2 H).

Example 128

Synthesis of 1{[2-(2-pyridinylethylnyl)-1-cyclopentene-1-yl]carbonyl}piperidine hydrochloride

To a stirred solution of 2-(2-pyridinylethylnyl)-1-cyclopentene-1-carboxylic acid from Example 127 (100 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) was added HOBT (95 mg, 0.70 mmol), EDCI (135 mg, 0.70 mmol), triethylamine (0.2 mL, 1.4 mmol) and piperidine (0.07 mL, 0.70 mmol) at 22°C. The reaction mixture was stirred for 18 h, then diluted with CH_2Cl_2 (50 mL). The organic phase was washed with sat. $NaHCO_3$ (2 x 25 mL) and sat. NaCl (2 x 25), dried ($MgSO_4$), filtered and concentrated in *vacuo* to give a yellow oil. Purification by flash chromatography on silica gel eluting with 1:1 hexane:ethyl acetate afforded 1{[2-(2-pyridinylethylnyl)-1-cyclopentene-1-yl]carbonyl}piperidine as a yellow oil which was treated with 1M HCl in diethyl ether (5 mL) to yield 1{[2-(2-pyridinylethylnyl)-1-cyclopentene-1-yl]carbonyl}piperidine hydrochloride as a yellow foam (40 mg, 27%). MS(ES): 281 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 8.75 (br, 1 H), 8.21 (br, 1 H), 7.74-7.73 (m, 2 H), 3.71 (m, 2 H), 3.53 (m, 2 H), 2.84-2.79 (m, 4 H), 2.11-2.05 (m, 2 H), 1.69-1.61 (m, 6 H).

Example 129

Synthesis of 1-methyl-4-{[2-(2-pyridinylethylnyl)-1-cyclopentene-1-yl]carbonyl}piperazine hydrochloride

To a stirred solution of 2-(2-pyridinylethylnyl)-1-cyclopentene-1-carboxylic acid from Example 127 (100 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) was added HOBT (95 mg, 0.70 mmol), EDCI (135 mg, 0.70 mmol), triethylamine (0.2 mL, 1.4 mmol) and 1-methylpiperazine (123 mg, 0.70 mmol) at 22°C. The reaction mixture was stirred for 18 h and then diluted with an additional amount of CH_2Cl_2 (50 mL). The organic phase was washed with sat. $NaHCO_3$ (2 x 25 mL) and sat. NaCl (2 x 25), dried

($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel eluting with 10:1 CH_2Cl_2:CH_3OH afforded 1-methyl-4-{[2-(2-pyridinylethylnyl)-1-cyclopentene-1-yl]carbonyl}piperazine as a yellow oil which was treated with 1M HCl in diethyl ether (5 mL) to yield 1-methyl-4-{[2-(2-pyridinylethylnyl)-1-cyclopentene-1-yl]carbonyl}piperazine hydrochloride as a yellow foam (130 mg, 78%). MS(ES): 296 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 8.66 (br, 1 H), 8.31 (br, 1 H), 7.82 (br, 2 H), 4.75 (m, 1 H), 4.10 (m, 2 H), 3.80 (m, 3 H), 3.36 (m, 2 H), 3.07 (s, 3 H), 2.79 (m, 4 H), 2.15 (m, 2 H).

Example 130

Synthesis of 4-(4-pyrimidinyl)phenyl trifluoromethanesulfonate

To a stirred solution of 4-(4-pyrimidinyl)phenol (250 mg, 1.45 mmol) in anhydrous CH_2Cl_2 (100 mL) was added triethylamine (0.4 mL, 2.9 mmol) followed by slow addition of trifluoromethanesulfonic anhydride (0.25 mL, 1.45 mmol) at 0°C under argon. The reaction mixture was allowed to warm to 22°C and stirred overnight and then diluted with CH_2Cl_2 (100 mL). The organic phase was washed with sat. NaCl (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a dark oil. Purification by flash chromatography on silica gel eluting with 4:1 hexane:ethyl acetate afforded 4-(4-pyrimidinyl)phenyl trifluoromethanesulfonate a brown oil (210 mg, 48%). MS(ES): 305 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 9.31-9.30 (d, J = 1.2 Hz, 1 H), 8.85-8.83 (m, 1 H), 8.22-8.19 (m, 2 H), 7.73 (m, 1 H), 7.46-7.43 (m, 2 H).

Example 131

Synthesis of 4-{4-[(2-methyl-1,3-thiazol-4-yl)ethynyl]phenyl}pyrimidine

A stirred solution of 4-(4-pyrimidinyl)phenyl trifluoromethanesulfonate from Example 130 (200 mg, 0.66 mmol) in DMF (8 mL) was degassed with argon for 10 min. $PdCl_2(Ph_3P)_2$ (46 mg, 0.07 mmol), CuI (38 mg, 0.2 mmol), triethylamine (0.23 mL, 1.64 mmol) and n-Bu_4NBr 243 mg, 0.66 mmol) were added, followed by 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (169 mg, 0.86 mmol). The reaction mixture was heated at 70°C under argon and then TBAF (1.0 M in THF, 0.86 mL, 0.86 mmol) was added slowly over 20 min. The reaction mixture was allowed to cool to 22°C, then filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to give the cross-coupled product 4-{4-[(2-methyl-1,3-thiazol-4-yl)ethynyl]phenyl}pyrimidine as a yellow solid. This material was treated with 1 M HCl in diethyl ether to afford a yellow solid (130 mg, 51%). M.P. 190-192°C. MS(ES): 278 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.53 (br, 1 H), 9.12 (br, 1 H), 8.57 (m, 1 H), 8.47 (s, 1 H), 8.45 (s, 1 H), 7.92 (s, 1 H), 7.84 (s, 1H), 7.81 (s, 1 H), 2.81 (s, 3 H).

Example 132

Synthesis of 3-bromo-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine & 3,5-bis[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

A solution of 3,5-dibromopyridine (5.1 g, 21.5 mmol) in DMF (100 mL) was degassed with argon for 10 min. $PdCl_2(Ph_3P)_2$ (0.75 g, 1.1 mmol), CuI (0.61 g, 3.2 mmol) and triethylamine (3.7 mL, 26.9 mmol) were added followed by 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (2.1 g, 10.7 mmol). The reaction mixture was heated at 73°C under argon. Then TBAF (1.0 M in THF, 11.8 mL, 11.8 mmol) was added slowly over 20 min. The reaction mixture was allowed to cool to 22°C, filtered through a pad of Celite™ and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 4:1 hexane:ethyl acetate to give two cross-coupled products: 3-bromo-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine as a white solid (1.7 g, 57%), M.P. 123-124°C, MS(ES): 280 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 8.69-8.68 (d, J = 1.7 Hz, 1 H), 8.63-8.23 (d, J = 2.2 Hz, 1 H), 7.99-7.98 (m, 1 H), 7.46 (s, 1 H), 2.76 (s, 3 H) ppm; and 3,5-bis[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine as a yellow solid (160 mg 5 %), M.P. 171-172°C, MS(ES): 322 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 8.72-8.71 (m, 2 H), 7.95 (m, 1 H), 7.46 (s, 2 H), 2.76 (s, 6 H).

Example 133

Synthesis of 3-(3-pyridinyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine hydrochloride

A solution of 3-bromo-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 132 (75 mg, 0.27 mmol) in THF (15 mL) was degassed with argon for 10 min. $Pd(Ph_3P)_4$ (15 mg, 0.013 mmol), KOH (45 mg, 0.81 mmol) and n-Bu_4NBr (43 mg, 0.13 mmol) were added, followed by diethyl(3-pyridyl)borane (51 mg, 0.35 mmol). The reaction mixture was heated at reflux for 5 h under argon, then allowed to cool to 22°C and filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with 2:1 ethyl acetate:hexane to give 3-(3-pyridinyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine as a brown oil. This material was treated with 1 M HCl in diethyl ether to yield 3-(3-pyridinyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine hydrochloride as a yellow solid (60 mg, 58%). M.P. 164-166°C. MS(ES): 278 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 8.97 (m, 1 H), 8.90 (d, 1.5 Hz, 1 H), 8.83-8.82 (d, 2.1 Hz, 1 H), 8.80-8.77 (m, 2 H), 8.30 (m, 1 H), 8.11 (m, 1 H), 7.82 (m, 1 H), 7.52 (s, 1 H), 7.27 (s, 1 H), 2.78 (s, 3 H).

Example 134

Synthesis of 3-(4-pyridinyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine hydrochloride

A solution of 3-bromo-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 132 (48 mg, 0.17 mmol) in 2:1 DME:H_2O (30 mL) was degassed with argon for 10 min. $Pd(Ph_3P)_4$ (10 mg, 0.009 mmol), K_2CO_3 (59 mg, 0.43 mmol) and n-Bu_4NBr (48 mg, 0.15 mmol) were added, followed by pyridine-4-boronic acid (32 mg, 0.26 mmol). The reaction mixture was heated at 90°C under argon for

1 h, then allowed to cool to 22°C, filtered through a pad of Celite™ and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 2:1 ethyl acetate:hexane to give 3-(4-pyridinyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine as a colorless oil. This material was treated with 1 M HCl in diethyl ether to afford 3-(4-pyridinyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine hydrochloride as a yellow solid (20 mg, 30%). M.P. 115-117°C. MS(ES): 278 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.48 (br, 1 H), 9.28 (br, 1 H), 9.18 (s, 1 H), 9.09 (s, 2 H), 8.63 (s, 2 H), 8.08 (s, 1 H), 2.83 (s, 3 H).

Example 135

Synthesis of 5-{5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-pyridinyl}pyrimidine hydrochloride

A solution of 3-bromo-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 132 (100 mg, 0.36 mmol) in 2:1 DMF:H_2O (5 mL) was degassed with argon for 10 min. $Pd(Ph_3P)_4$ (21 mg, 0.018 mmol), K_2CO_3 (124 mg, 0.9 mmol) and n-Bu_4NBr (115 mg, 0.36 mmol) were added, followed by 5-pyrimidinylboronic acid (67 mg, 0.54 mmol). The reaction mixture was heated at 90°C under argon for 1 h, then allowed to cool to 22°C and filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with 2:1 ethyl acetate:hexane to give 5-{5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-pyridinyl}pyrimidine as a colorless oil. This material was treated with 1 M HCl in diethyl ether to afford 5-{5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-pyridinyl}pyrimidine hydrochloride as a yellow solid (20 mg, 30%). M.P. 135-137°C. MS(ES): 279 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.37-8.77 (m, 5 H), 7.97 (m, 1 H), 7.73 (m, 1 H), 2.78-2.77 (d, J = 1.6 Hz, 3 H).

Example 136

Synthesis of 3-(3,5-dimethyl-4-isoxazolyl)-5-[(2-methyl-1,3-thiazo-4-yl)ethynyl]pyridine hydrochloride

A solution of 3-bromo-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 132 (100 mg, 0.36 mmol) in 2:1 DMF:H_2O (5 mL) was degassed with argon for 10 min. $Pd(Ph_3P)_4$ (21 mg, 0.018 mmol), K_2CO_3 (124 mg, 0.9 mmol) and n-Bu_4NBr (115 mg, 0.36 mmol) were added followed by 3,5-dimethyl-4-isoxazolylboronic acid (78 mg, 0.54 mmol). The reaction mixture was heated at 90°C under argon overnight, allowed to cool to 22°C and filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with 2:1 hexane:ethyl acetate to give 3-(3,5-dimethyl-4-isoxazolyl)-5-[(2-methyl-1,3-thiazo-4-yl)ethynyl]pyridine as a yellow solid. This material was treated with 1 M HCl in diethyl ether to afford 3-(3,5-dimethyl-4-isoxazolyl)-5-[(2-methyl-1,3-thiazo-4-yl)ethynyl]pyridine hydrochloride as a yellow solid (19 mg, 13%). MS(ES): 296 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.20-8.81 (m, 3 H), 8.01 (br, 1 H), 2.80 (s, 3 H), 2.58 (s, 3 H), 2.39 (s, 3 H).

Example 137

Synthesis of 3-(4-methoxyphenyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine hydrochloride

A solution of 3-bromo-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine from Example 132 (100 mg, 0.36 mmol) in 2:1 DMF:H_2O (5 mL) was degassed with argon for 10 min. $Pd(Ph_3P)_4$ (21 mg, 0.018 mmol), K_2CO_3 (124 mg, 0.9 mmol) and n-Bu_4NBr (115 mg, 0.36 mmol) were added followed by 4-methoxyphenylboronic acid (82mg, 0.54 mmol). The reaction mixture was heated at 90°C under argon for 1 h, then allowed to cool to 22°C and filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to give 3-(4-methoxyphenyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine as a yellow solid. This material was treated with 1 M HCl diethyl ether to afford 3-(4-methoxyphenyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine hydrochloride as a yellow foam (90 mg, 66%). MS(ES): 307 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.12 (s, 1 H), 9.00-8.98 (m, 2 H), 7.96 (s, 1 H), 7.84 (s, 1 H), 7.81 (s, 1 H), 7.17 (s, 1 H), 7.14 (s, 1 H), 3.89 (s, 3 H), 2.76 (s, 3 H).

Using the synthetic and purification procedures described in Examples 132 to 137, and using the appropriate reagents, compounds described in Examples 138 to 145 were prepared.

Example 138

3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-5-(2-thienyl)pyridine

Isolated as an off white solid. M.P 175-176°C. MS(ES): 283 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.16 (br, 1 H), 8.92-8.91 (m, 2 H), 7.96 (s, 1 H), 7.86-7.84 (m, 1 H), 7.77-7.75 (m, 1 H), 7.28-7.26 (m, 1 H), 2.78 (s, 3 H).

Example 139

3-(2-Furyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

Isolated as a colorless glass. MS(ES): 267 (M+H)+, ^{1}H NMR ($CDCl_3$) δ: 8.87 (m, 1 H), 8.64 (m, 1 H), 8.10-8.08 (m, 1 H), 7.54-7.54 (m, 1 H), 7.46 (s, 1 H), 8.78-6.77 (m, 1 H), 6.53 (m, 1 H), 2.76 (s, 3 H).

Example 140

3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-5-(4-(trifluoromethyl)phenyl]pyridine

Isolated as an off-white foam. MS(ES): 267 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.13 (br, 1 H), 9.02 (br, 1 H), 8.85 (br, 1 H), 8.03 (s, 1 H), 8.00 (s, 1 H), 7.91 (s, 2 H), 7.88 (s, 1 H), 2.75 (s, 3 H).

Example 141

3-(1-Benzothien-2-yl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

Isolated as an off-white solid. MS(ES): 333 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.12 (br, 1 H), 8.84 (br, 1 H), 8.70 (s, 1 H), 8.03 (s, 1 H), 7.92-7.90 (m, 3 H), 7.45-7.42 (m, 2 H), 2.76 (s, 3 H).

Example 142

3-(2-Methyl-1,3-thiazol-4-yl)-5-(1H-pyrazol-3-yl)pyridine

Isolated as an off-white solid. M.P. 184-186°C, MS(ES): 267 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.28 (s, 1 H), 9.13 (s, 1 H), 9.01 (s, 1 H), 8.03 (s, 1 H), 7.88-7.87 (d, J = 2.25 Hz, 1 H), 7.07-7.06 (d, J = 2.25 Hz, 1 H), 2.80 (s, 3 H).

Example 143

3-(2,4-Difluorophenyl)-5-(2-methyl-1,3-thiazol-4-yl)pyridine

Isolated as a white solid. MS(ES): 313 (M+H)+, ^{1}H NMR (CD_3OD) δ: 8.87 (br, 2 H), 8.45 (br, 1 H), 7.86 (s, 1 H), 7.72-7.68 (m, 1 H), 7.24-7.16 (m, 2 H), 2.74 (s, 3 H)

Example 144

3-(4-Fluorophenyl)-5-(2-methyl-1,3-thiazol-4-yl)pyridine

Isolated as a low melting/hygroscopic solid. MS(ES): 295 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.16 (m, 1 H), 9.06 (m, 1 H), 9.10 (m, 1 H), 7.96 (s, 1 H), 7.93-7.89 (m, 2 H), 7.39-7.33 (m, 2 H), 2.76 (s, 3 H).

Example 145

3-(2-methyl-1,3-thiazol-4-yl) -5-phenylpyridine

Isolated as a hygroscopic solid. MS(ES): 277 (M+H)+, ^{1}H NMR (CD_3OD) δ: 9.10 (br, 2 H), 8.76 (s, 1 H), 7.90 (s, 1 H), 7.82-7.79 (m, 2 H), 7.60-7.54 (m, 3 H), 2.75 (s, 3 H).

Example 146

Synthesis of 2-fluorocyclohexanone

To a stirred solution of (1-cyclohexen-1-yloxy)(trimethyl)silane (3.5 g, 21 mmol) in dry MeCN (200 mL) under argon was added Selectfluor reagent (8.0 g, 23 mmol). The mixture was stirred at ambient temperature for 3 h, then stored at -20°C overnight, at which time GC/MS showed the reaction to be complete. The mixture was diluted with ethyl acetate (600 mL), washed with dilute brine (300 mL) and then saturated brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting liquid was purified by Kugelrohr distillation (130°C air bath at 20 Torr) to afford 2-fluorocyclohexanone (1.6 g, 67%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.90 (ddd, $J_{1(HF)}$=49.1 Hz, J_2=11.3 Hz, J_3=6.4 Hz, 1H), 2.61-1.67 (m, 8H). MS (EI ionization) 116 (M^+).

Example 147

Synthesis of 2-fluoro-1-[(trimethylsilyl)ethynyl]cyclohexanol

A solution of n-BuLi (7.6 mL, 2.2M in hexanes, 17 mmol) was added slowly at -40°C to a stirred solution of trimethylsilylacetylene (2.3 mL, 16 mmol) in dry THF (30 mL) under argon. The mixture was stirred at -40°C for 20 min, cooled to -78°C, then a solution of 2-fluorocyclohexanone

from Example 146 (1.6 g, 14 mmol) in dry THF (20 mL) was added via syringe. The mixture was warmed to ambient temperature gradually over 1 h and then stirred at ambient temperature for 4 h. Analysis of the reaction mixture by GC/MS at this time showed the reaction to be complete. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL), stirred for 5 min, then poured into H_2O (50 mL), and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-fluoro-1-[(trimethylsilyl)ethynyl]cyclohexanol (3.4 g, 97%) as a light brown oil as a mixture of diastereomers. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.89-1.25 (m, 10H), 0.15 (s, 9H). MS (EI ionization) 214 (M^+).

Example 148

Synthesis of 2-fluoro-1-(1,3-thiazol-2-ylethynyl)cyclohexanol

$PdCl_2$ (45 mg, 0.25 mmol) was suspended in DME (20 mL), then argon was bubbled through the solution for several min to deoxygenate it. H_2O (6.6 mL), K_2CO_3 (4.5 g, 32 mmol), CH_3OH (20 mL), 2-bromo-1,3-thiazole (2.63 g, 16.1 mmol), PPh_3 (280 mg, 1.07 mmol) and CuI (204 mg, 1.07mmol) were then added and the reaction mixture was heated to 50°C. After a few min 2-fluoro-1-[(trimethylsilyl)ethynyl]cyclohexanol from Example 147 (2.3 g, 11 mmol) was added to the dark brown suspension. The reaction was then heated to 60°C and after 16 h at 60°C, GC/MS showed no remaining 2-bromo-1,3-thiazole. The reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate (200 mL), and filtered through Celite™. The filter pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel on silica gel eluting with hexane, 9:1, then 7.5:2.5 hexane:ethyl acetate to afford 2-fluoro-1-(1,3-thiazol-2-ylethynyl)cyclohexanol (1.1 g, 45%) as a yellowish solid, and a 5:1 mixture of diastereomers. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J=3 Hz, 1H), 7.37 (d, J=3 Hz, 1H), 4.80-4.33 (m, 1H), 3.06 (s, 1H), 2.21-1.23 (m, 6H). MS (EI ionization) 225 (M^+).

Example 149

Synthesis of 3-ethoxy-5-methyl-2-cyclohexen-1-one

A solution of 5-methyl-1,3-cyclohexanedione (9.83 g, 77.9 mmol) and $TsOH•H_2O$ (636 mg, 6 wt.%) in ethanol (80 mL) was heated to reflux. After 15 min, triethyl orthoformate (5 mL, 30 mmol) was added. After 10min TLC showed the reaction was incomplete, and additional triethyl orthoformate (5 mL, 30 mmol) was added. After a further 10 min GC/MS showed the reaction to be complete. The reaction mixture was concentrated *in vacuo*, then diluted with diethylether (300 mL) and washed with $NaHCO_3$, H_2O (300 mL), brine (2 x 300 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, to afford 3-ethoxy-5-methyl-2-cyclohexen-1-one as an yellowish-orange oil

(11.04 g, 92%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 5.34 (s, 1H), 3.94-3.86 (m, 2H), 2.44-1.95 (m, 6H), 1.36 (t, J=7 Hz, 3H), 1.08 (d, J=6 Hz, 3H). MS (EI ionization) 154 (M^+).

Example 150

Synthesis of 5-methyl-3-(2-pyridinylethynyl)-2-cyclohexen-1-one

A solution of n-BuLi (8 mL, 2.2M in hexanes, 18 mmol) was added slowly at 0°C to a stirred solution of diisopropylamine (2.8 mL, 19 mmol) in dry THF (20 mL) under argon. The mixture was stirred at 0°C for 30 min then a solution of 2-ethynylpyridine (2.27 g, 22.0 mmol) in dry THF (20 mL) was added via syringe. The mixture was stirred at 0°C for 1 h, then 5-methyl-3-ethoxy-2-cyclohexene-1-one from Example 149 (2.0 g, 13 mmol) was added. After stirring for 16 h at ambient temperature GC/MS showed the reaction was complete. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL), stirred for 5 min and poured into H_2O (50 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel eluting with hexane, 9:1, 4:1, then 7:3 hexane:ethyl acetate to afford 5-methyl-3-(2-pyridinylethynyl)-2-cyclohexen-1-one (1.0 g, 36%) as a light green solid. M.p.= 62.5-65°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, J=6 Hz, 1H), 7.74-7.68 (m, 1H), 7.51 (d, J=9 Hz, 1H), 7.32-7.26 (m, 1H), 6.37 (s, 1H), 2.67-2.50 (m, 2H), 2.33-2.09 (m, 3 H), 1.11 (d, 3H). MS (ESI) 212.0 (M^++H).

Example 151

Synthesis of 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one

To a solution of 5,5-dimethyl-1,3-cyclohexanedione (25.2 g, 180 mmol) in ethanol (200 mL), was added TsOH• H_2O (1.06 g, 4.2 wt%), then triethyl orthoformate (30 mL, 180 mmol). The resulting pale yellow solution was then heated to reflux. After heating for 15 min the solution had turned bright orange. GC/MS analysis of the reaction after 1 h showed no starting material present. The orange-brown solution was concentrated *in vacuo*, diluted with ethyl acetate (300 mL), washed with saturated aqueous $NaHCO_3$ (2 x 75 mL), brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford an orange semi-solid. The crude product was purified by column chromatography on silica gel eluting with hexane, then 3:1 hexane:ethyl acetate to afford 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one (13.5 g, 44%) as an orange oil that slowly solidified. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.34 (s, 1H), 3.90 (q, J=7.0 Hz, 2H), 2.28 (s, 1H), 2.21 (s, 1H), 1.37 (t, J=7.0 Hz, 3H), 1.08 (s, 6H). MS (EI ionization) 168 (M^+).

Example 152

Synthesis of 5,5-dimethyl-3-(2-pyridinylethynyl)-2-cyclohexen-1-one

A solution of n-BuLi (7.0 mL, 2.2M in hexanes, 15 mmol) was added slowly at 0°C to a stirred solution of diisopropylamine (2.5 mL, 18 mmol) in dry THF (20 mL) under argon. The mixture was stirred at 0°C for 30 min then a solution of 2-ethynylpyridine (2.1 g, 20mmol) in dry THF (20 mL) was added via syringe. The mixture was stirred at 0°C for 1 h then 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one from Example 151 (2.0 g, 12 mmol) was added and the reaction mixture was allowed to warm to ambient temperature. After 16 h at ambient temperature GC/MS showed the reaction to be complete. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL). After 5 min the reaction was poured into H_2O (50 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel eluting with hexane, 9:1, then 4:1 hexane:ethyl acetate to afford 5,5-dimethyl-3-(2-pyridinylethynyl)-2-cyclohexen-1-one (0.563 g, 12%) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, J=6 Hz, 1H), 7.72-7.71 (m, 1H), 7.51 (d, J=6 Hz, 1H), 7.28-7.27 (m, 1H), 6.38 (s, 1H), 2.47 (s, 2H), 2.31 (s, 2H), 1.09 (s, 6H). MS (ESI) 226.1 (M^++H).

Example 153

Synthesis of 2-[(trimethylsilyl)ethynyl]bicyclo[2.2.1]heptan-2-ol

A solution of n-BuLi (46 mL of a 2.2M solution in hexanes, 100 mmol) was added slowly at -78°C to a stirred solution of trimethylsilylacetylene (10 g, 100 mmol) in dry THF (100 mL) under argon. The mixture was stirred at -78°C for 30 min, then a solution of bicyclo[2.2.1]heptan-2-one (norcamphor) (7.7 g, 70 mmol) in dry THF (70 mL) was added via syringe. The mixture was allowed to reach ambient temperature gradually and stirred for 1.5 hr, at which time GC/MS showed the reaction to be complete. The reaction was quenched by the addition of saturated aqueous NH_4Cl (300 mL), the mixture was stirred for 5 min and poured into H_2O (100 mL), and extracted with ethyl acetate (3 x 300 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, and filtered. The crude material was purified by column chromatography on silica gel eluting with hexane, then 20:1 hexane:ethyl acetate to afford 2-[(trimethylsilyl)ethynyl]bicyclo[2.2.1]heptan-2-ol (10 g, 47%) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06-1.31 (m, 11H), 0.16 (s, 9H). MS (EI ionization) 207.

Example 154

Synthesis of 2-(1,3-thiazol-2-ylethynyl)bicyclo[2.2.1]heptan-2-ol

$PdCl_2$ (27 mg, 0.15mmol) was suspended in DME (20 mL), then argon was bubbled through the solution for several min to deoxygenate it. H_2O (10 mL), K_2CO_3 (2.5 g, 18 mmol), CH_3OH (20 mL), 2-bromo-1,3-thiazole (1.0 g, 6.1 mmol), PPh_3 (160 mg, 0.61 mmol) and CuI (118 mg, 0.61 mmol) were

added and the reaction was heated to 50°C. After a few min 2-[(trimethylsilyl)ethynyl]-bicyclo[2.2.1]heptan-2-ol from Example 153 (1.3 g, 6.1 mmol) was added to the dark brown suspension. The reaction was heated to 60°C and allowed to stir for 16 h, at which time GC/MS showed no remaining 2-bromo-1,3-thiazole. The reaction mixture was diluted with ethyl acetate (200 mL), and filtered through Celite™. The filter pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexane, 9:1, then 4:1 hexane:ethyl acetate to afford 2-(1,3-thiazol-2-ylethynyl)bicyclo[2.2.1]heptan-2-ol (550 mg, 42%) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J=3 Hz, 1H), 7.34 (d, J=3 Hz, 1H), 2.55-1.26 (m, 11H). MS (EI ionization) 219.

Example 155

Synthesis of 2-(bicyclo[2.2.1]hept-2-en-2-ylethynyl)-1,3-thiazole

To a solution of 2-(1,3-thiazol-2-ylethynyl)bicyclo[2.2.1]heptan-2-ol from Example 154 (300 mg, 1.37 mmol) in CH_2Cl_2 (20 mL) under argon, was added a catalytic amount of 4-(dimethylamino)-pyridine, and triethylamine (0.57 mL, 4.1 mmol). After 2 min methanesulfonyl chloride (0.16 mL, 2.0 mmol) was added. After 1 h GC/MS showed the reaction to be complete. The mixture was diluted with ethyl acetate (200 mL), and washed with $NaHCO_3$ (200 mL), H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexane, then 98:2 hexane:ethyl acetate to afford 2-(bicyclo[2.2.1]hept-2-en-2-ylethynyl)-1,3-thiazole (203 mg, 74%) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, J=3 Hz, 1H), 7.33 (d, J=3 Hz, 1H), 6.55 (d, J=3 Hz, 1H), 3.09 (s, 1H), 2.99 (d, J=1.2 Hz, 1H) 1.81-1.67 (m, 2 H), 1.53 (d, J=8.5 Hz, 1H), 1.25-1.09 (m, 3H). MS (ESI) 202.1 (M^++H).

Example 156

Synthesis of 1-[(6-methyl-2-pyridinyl)ethynyl]cyclopentanol

$PdCl_2(PPh_3)_2$ (320 mg, 0.45 mmol) was suspended in DME (20 mL) then argon was bubbled through the solution for several min to deoxygenate it. 2-Bromo-6-methylpyridine (1.9 g, 11 mmol), triethylamine (6.3 mL, 45 mmol) and CuI (170 mg, 0.91 mmol) were added and the reaction was heated to 50°C. After a few min 1-ethynyl cyclopentanol (1.0 g, 9.1 mmol) was added to the dark brown suspension. The reaction was heated to 60°C, and after 16 h at 60°C GC/MS and TLC analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (200 mL), and filtered through Celite™. The filter pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexane, 9:1, 8:2, then 7:3 hexane:ethyl acetate to afford 1-[(6-methyl-2-pyridinyl)ethynyl]cyclopentanol (1.2 g, 57%) as a yellow solid. MS (EI ionization) 201 (M^+).

Example 157

Synthesis of 2-(1-cyclopenten-1-ylethynyl)-6-methylpyridine

To a solution of 1-[(6-methyl-2-pyridinyl)ethynyl]cyclopentanol from Example 156 (190 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) under argon was added phosphorus pentoxide (355 mg, 2.5 mmol). The mixture was allowed to stir at ambient temperature for 16 h at which time TLC showed the reaction to be complete. The reaction was quenched by the addition of saturated aqueous Na_2CO_3 solution (to basic pH), stirred for 5 min, and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel eluting with hexane, then 9:1 hexane:ethyl acetate to afford 2-(1-cyclopenten-1-ylethynyl)-6-methylpyridine (110 mg, 63%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54-7.48 (m, 1H), 7.25-7.23 (m, 1H) 7.07-7.03 (m, 1H), 6.25-6.23 (m, 1H), 2.60-2.43 (m, 7H), 1.99-1.90 (m, 2H). MS (ESI) 184.1 (M^++H).

Example 158

Synthesis of Racemic 2-{[(cis)-3,4-dimethyl-1-cyclopenten-1-yl]ethynyl}pyridine

A solution of n-BuLi (16.8 mL of a 2.5M solution in hexanes, 42.0 mmol) was added gradually at 0°C to a stirred solution of diisopropylamine (5.9 mL, 42 mmol) in dry THF (40 mL) under argon. The mixture was stirred at 0°C for 30 min then cooled to -78°C and a solution of cis-3,4-dimethylcyclopentanone [Mori, K., Ueda, H.; Tetrahedron, (1982), pp 1227-1233] (3.6 g, 32 mmol) in dry THF (20 mL) was added via syringe. After the mixture stirred at -78°C for 1 h a solution of N-phenyltrifluoromethanesulfonimide (13.8 g, 38.6 mmol) in dry THF (40 mL) was added via syringe during 15 min. The reaction was allowed to warm gradually to ambient temperature, and after stirring for 16 h at ambient temperature GC/MS showed no remaining cis-3,4-dimethylcyclopentanone. The reaction was quenched with $NaHCO_3$ (2mL), DME (30 mL) was added, and argon was bubbled through the solution for several min to deoxygenate it. To the resulting solution of racemic (cis)-3,4-dimethyl-1-cyclopenten-1-yl trifluoromethanesulfonate $PdCl_2(PPh_3)_2$ (1.1 g, 1.6 mmol), triethylamine (22 mL, 160 mmol), CuI (1.2 g, 6.4 mmol), Ph_3P (0.50 g, 1.9 mmol), and 2-ethynylpyridine (4.0 g, 38 mmol) were added, and the reaction was heated to 50°C. After stirring for 16 h at 50°C, TLC analysis showed no remaining racemic (cis)-3,4-dimethyl-1-cyclopenten-1-yl trifluoromethanesulfonate. The mixture was diluted with ethyl acetate (400 mL), and filtered through a Celite™ pad. The filter pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexane, then 96:4 hexane:ethyl acetate to afford racemic 2-{[(cis)-3,4-dimethyl-1-cyclopenten-1-yl]ethynyl}pyridine (4.6 g, 73%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58-8.56 (m, 1H), 7.66-7.60 (m, 1H) 7.42 (d, J=9 Hz, 1H), 7.22-7.17 (m, 1H), 6.18-6.15 (m, 1H), 2.82-2.11 (m, 4H), 0.98-0.91 (m, 6H). MS (ESI) 198.1 (M^++H).

Example 159

Synthesis of 2-{[(3S,4R)-3,4-dimethyl-1-cyclopenten-1-yl]ethynyl}pyridine

A solution of n-BuLi (6.7 mL of a 2.5M solution in hexanes, 17 mmol) was added slowly to a stirred solution of diisopropylamine (2.4 mL, 17 mmol) in dry THF (20 mL) at 0°C under argon. The mixture was stirred at 0°C for 30 min then cooled to -78°C and a solution of (3*S*,4*S*)-3,4-dimethylcyclopentanone [Kokke, W. C. M. C., Varkevisser, F. A.; J. Org. Chem. (1974), pp 1535-1539; Heathcock, C. H., Davis, B. R., Hadley, C. R.; J. Med. Chem. (1989), pp 197-202) (1.45 g, 13.0 mmol] in dry THF (10 mL) was added via syringe. After the mixture was stirred at -78°C for 1 h, a solution of N-phenyltrifluoromethanesulfonimide (5.5 g, 16mmol) in dry THF (20 mL) was added via syringe during 15 min. The reaction was stirred and allowed to gradually warm to ambient temperature. After stirring for 16 h, GC/MS showed no remaining (3*S*,4*S*)-3,4-dimethylcyclopentanone. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), DME (15 mL) was added, then argon was bubbled through the solution for several min to deoxygenate it. To the resulting solution of (3*R*,4*S*)-3,4-dimethyl-1-cyclopenten-1-yl trifluoromethanesulfonate $PdCl_2(PPh_3)_2$ (460 mg, 0.65 mmol), triethylamine (9.0 mL, 65 mmol), CuI (0.50 g, 2.6 mmol), Ph_3P (0.46 g, 0.65 mmol), and 2-ethynylpyridine (1.3 g, 13 mmol) were added and the reaction was heated to 50°C. After stirring for 16 h at 50°C, TLC showed no remaining (3*R*,4*S*)-3,4-dimethyl-1-cyclopenten-1-yl trifluoromethanesulfonate. The mixture was diluted with ethyl acetate (200 mL), and filtered through Celite™. The filter pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexane, then 98:2, then 96:4 hexane:ethyl acetate to afford 2-{[(3*S*,4*R*)-3,4-dimethyl-1-cyclopenten-1-yl]ethynyl}pyridine (1.5 g, 64%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (m, 1H), 7.66-7.60 (m, 1H) 7.41 (d, J=9 Hz, 1H), 7.21-7.18 (m, 1H), 6.09 (d, J=3 Hz, 1H), 2.74-1.85 (m, 4H), 1.09-1.04 (m, 6H). MS (ESI) 198.1 (M^++H).

Example 160

Synthesis of Racemic 2-{[(trans)-3,4-dimethyl-1-cyclopenten-1-yl]ethynyl}pyridine

A cis-trans mixture of 2-[(3,4-dimethyl-1-cyclopenten-1-yl)ethynyl]pyridine was separated by preparative reverse phase HPLC (Zorbax SB-C18 15cm x 21 mm x 5μm dp; Mobile phase A: 100:0.1 H_2O:TFA, Mobile phase B: 100:0.1 acetonitrile:TFA; 30% B at 20 mL/min.) The resulting trifluoroacetic acid salt of the *trans* isomer was suspended in aqueous K_2CO_3 and the resulting aqueous suspension was extracted with ethyl acetate. The aqueous layer was then saturated with solid NaCl and extracted with ethyl acetate (5 x 100 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a brown oil. The dark product was further purified by column chromatography on silica gel eluting with 6:1 then 4:1 hexane:ethyl acetate to afford racemic 2-{[(trans)-3,4-dimethyl-1-cyclopenten-1-yl]ethynyl}pyridine (155.3 mg) as a pale yellow oil. ^{1}H NMR

($CDCl_3$, 300 MHz) δ 8.58-8.56 (m, 1H), 7.66-7.59 (m, 1H), 7.43-7.40 (m, 1H), 7.22-7.16 (m, 1H), 6.12-6.10 (m, 1H), 2.79-2.71 (m, 1H), 2.42-2.35 (m, 1H), 2.25-2.16 (m, 1H), 1.91-1.85 (m, 1H), 1.07 (t, J=7.0 Hz, 6H). MS (ESI) 198.1 (M^++H).

Example 161

Synthesis of 2-methyl-4-(1,3-thiazol-2-ylethynyl)-1,3-thiazole

CuI (50 mg, 0.26 mmol), $PdCl_2(PPh_3)_2$ (93 mg, 0.13 mmol), PPh_3 (70 mg, 0.26 mmol), and tetrabutylammonium iodide (377 mg, 1.02 mmol) were combined in dry DMF (20 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (0.8 mL, 5 mmol), was added, and the reaction mixture was warmed to 40°C, then a solution of 2-bromo-1,3-thiazole (218 mg, 1.32 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (200 mg, 1.02 mmol) in DMF (10 mL) added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (1.3 mL of a 1.0M solution in THF, 1.3 mmol) was added by syringe pump over 1 h. After stirring for an additional 2 h, GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (30 mL), filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 9:1, 4:1, then 3:1 hexane:ethyl acetate to afford 2-methyl-4-(1,3-thiazol-2-ylethynyl)-1,3-thiazole (165 mg, 78%) as a brown solid. M.p.= 57-58°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, J=3.0 Hz, 1H), 7.55 (s, 1H), 7.41 (d, J=3.0 Hz, 1H), 2.76 (s, 3H). MS (ESI) 207.0 (M^++H).

Example 162

Synthesis of 4-(3-pyridinylethynyl)-1,3-thiazol-2-amine

CuI (51 mg, 0.26 mmol), $PdCl_2(PPh_3)_2$ (93 mg, 0.13 mmol), PPh_3 (70 mg, 0.26 mmol), tetrabutylammonium iodide (377 mg, 1.02 mmol) were combined in dry DMF (20 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (0.8 mL, 5 mmol), was added, the reaction mixture was warmed to 40°C, then a solution of 3-bromopyridine (210 mg, 1.32 mmol) and 4-[(trimethylsilyl)ethynyl]-1,3-thiazol-2-ylamine from Example 78 (200 mg, 1.02 mmol) in DMF (10 mL) added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (1.3 mL of a 1.0M solution in THF, 1.3 mmol) was added by syringe pump over 1 h. After stirring for an additional 2 h, GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (30 mL), filtered through Celite™, and the filter pad washed thoroughly with ethyl acetate. The combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 4:1, 1:1, then 1:4 hexane:ethyl acetate. The product was further purified by recrystallization from hot $CHCl_3$ to afford 4-(3-pyridinylethynyl)-1,3-thiazol-2-amine (90 mg, 43%) as

a brown solid. M.p.= 165-170°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (s, 1H), 8.50 (d, J=6.0 Hz, 1H), 7.95-7.92, (m, 1H), 7.47-7.44 (m, 1H), 6.93 (s, 1H). MS (EI ionization) 201.0 (M^+).

Example 163

Synthesis of 4-[(2-methyl-1,3-thiazol-4-yl)ethynyl]isothiazole

CuI (60.0 mg, 0.31 mmol), $PdCl_2(PPh_3)_2$ (109 mg, 0.15 mmol), PPh_3 (82 mg, 0.31 mmol), and tetrabutylammonium iodide (440 mg, 1.2 mmol) were combined in dry DMF (20 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (0.8 mL, 5 mmol), was added, and the reaction mixture was warmed to 40°C, then a solution of 4-bromoisothiazole (200 mg, 1.2 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (360 mg, 1.8 mmol) in DMF (10 mL) was added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (1.6 mL of a 1.0M solution in THF, 1.6 mmol) was added by syringe pump over 1 h. After stirring for an additional 2 h, GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (30 mL) and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 9:1, then 4:1 hexane:ethyl acetate to afford 4-[(2-methyl-1,3-thiazol-4-yl)ethynyl]isothiazole (140 mg, 37%) as a yellow solid. M.p.= 113-114°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.79 (s, 1H), 8.61 (s, 1H), 7.41 (s, 1H), 2.75 (s, 3H). MS (ESI) 207.0 (M^++H).

Example 164

Synthesis of 2-methyl-4-(1,3-thiazol-4-ylethynyl)-1,3-thiazole

CuI (60 mg, 0.31 mmol), $PdCl_2(PPh_3)_2$ (110 mg, 0.15 mmol), PPh_3 (82 mg, 0.31 mmol), and tetrabutylammonium iodide (440 mg, 1.2 mmol) were combined in dry DMF (20 mL), and argon gas was bubbled through the suspension for several min to deoxygenate it. Triethylamine (0.8 mL, 5 mmol), was added, the reaction mixture was warmed to 40°C, then a solution of 4-bromo-1,3-thiazole (200 mg, 1.2 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (360 mg, 1.8 mmol) in DMF (10 mL) was added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (1.6 mL of a 1.0M solution in THF, 1.6 mmol) was added via syringe pump over 1 h. After stirring for an additional 2 h, GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (30 mL) and filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 9:1, 4:1, then 3:1 hexane:ethyl acetate to afford 2-methyl-4-(1,3-thiazol-4-ylethynyl)-1,3-thiazole (112 mg, 30%) as a yellow solid. M.p.= 102-103°C. ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 8.82 (d, J=2 Hz, 1H), 7.64 (d, J=2 Hz, 1H), 7.46 (s, 1H), 2.75 (s, 3H). MS (ESI) 207.0 (M^++H).

Example 165

Synthesis of 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]isothiazole

CuI (60 mg, 0.31 mmol), $PdCl_2(PPh_3)_2$ (110 mg, 0.15 mmol), PPh_3 (82 mg, 0.31 mmol), and tetrabutylammonium iodide (440 mg, 1.2 mmol) were combined in dry DMF (20 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (0.8 mL, 5 mmol), was added, and the reaction mixture was warmed to 40°C, then a solution of 5-bromoisothiazole (200 mg, 1.2 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (360 mg, 1.8 mmol) in DMF (10 mL) was added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (1.6 mL of a 1.0M solution in THF, 1.6 mmol) was added by syringe pump over 1 h. After stirring for an additional 2 h, GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (30 mL) and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 9:1, then 4:1 hexane:ethyl acetate to afford 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]isothiazole (160 mg, 42%) as a yellow solid. M.p.= 79-80°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (d, J=2 Hz, 1H), 7.48 (s, 1H), 7.39, (d, J=2 Hz, 1H), 2.75 (s, 3H). MS (ESI) 207.0 (M^++H).

Example 166

Synthesis of 2-([1,1'-biphenyl]-4-ylethynyl)pyrimidine

CuI (84 mg, 0.44 mmol), $PdCl_2(PPh_3)_2$ (155 mg, 0.22 mmol), PPh_3 (110 mg, 0.44 mmol), and tetrabutylammonium iodide (630 mg, 1.7 mmol) were combined in dry DMF (25 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (1 mL, 8 mmol), was added, and the reaction mixture was warmed to 40°C, then a solution of 4-bromobiphenyl (515 mg, 2.2 mmol) and 2-[(trimethylsilyl)ethynyl]pyrimidine from Example 81 (300 mg, 1.7 mmol) in DMF (10 mL) was added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (2.2 mL of a 1.0M solution in THF, 2.2 mmol) was added by syringe pump over 2 h. After stirring for an additional 2 h, GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (50 mL) and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 9:1, then 8.5:1.5 hexane:ethyl acetate to afford 2-([1,1'-biphenyl]-4-ylethynyl)pyrimidine (200 mg, 46%) as a yellow solid. The product was dissolved in diethyl ether (20 mL) and HCl in diethyl ether (12 mL of a 1.0M solution, 12 mmol) was added to afford a light yellow precipitate. The

precipitate was filtered, and dried *in vacuo* to afford 2-([1,1'-biphenyl]-4-ylethynyl)pyrimidine hydrochloride (170 mg, 34%) as a yellow solid. M.p.= 135-137°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.01 (d, J=6 Hz, 2H), 7.76-7.66 (m, 7H), 7.49-7.39, (m, 3H). MS (ESI) 257.0 (M+H).

Example 167

Synthesis of N'-{3-[2-(2-pyridinyl)ethynyl]-2-cyclohexen-1-ylidene}-2-furohydrazide

A solution of 2-furohydrazide (61 mg, 0.48 mmol) in ethanol (1 mL) was treated with acetic acid (1 drop), and 3-(2-pyridinylethynyl)-2-cyclohexen-1-one from Example 104 (86 mg, 0.44 mmol) was added as a solution in ethanol (1 mL) followed by a rinse of the flask and syringe (0.5 mL). The resulting solution was then heated in a 90°C oil bath for 45 min. The reaction solution was cooled to ambient temperature and concentrated *in vacuo* to afford an orange oil. The crude oil was adsorbed onto silica gel and purified by column chromatography on silica gel eluting with 40:1 $CHCl_3$:CH_3OH to afford *N'*-{3-[2-(2-pyridinyl)ethynyl]-2-cyclohexen-1-ylidene}-2-furohydrazide (40.2 mg, 30%) as a yellow oil. The material appeared to be one component by LC/MS analysis, but showed some extra peaks in the NMR spectra possibly caused by a mixture of double bond isomers being present. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.56 (br s, 0.1 H), 9.33 (br s, 0.9H), 8.60 (d, 1H, J=4.7 Hz), 7.68 (t, 1H, J=8.6 Hz), 7.55-7.43 (m, 2H), 7.35-7.20 (m, 2H), 6.96 (br s, 0.1H), 6.86 (br s, 0.9H), 6.56 (dd, J=1.6, 3.5 Hz, 1H), 2.67-2.62 (m, 0.1H), 2.56-2.40 (m, 3.8H), 2.26 (br s, 0.2H), 2.03-1.93 (m, 1.8H). MS (ESI) 306.1 (M^++H).

Example 168

Synthesis of N-{4-[2-(1-cyclohexen-1-yl)ethynyl]-1,3-thiazol-2-yl}benzamide

To a suspension of 4-(1-cyclohexen-1-ylethynyl)-1,3-thiazol-2-ylamine tosylate from Example 41 (65 mg, 0.17 mmol) in THF (2.0 mL) was added triethylamine (0.10 mL, 0.72 mmol) to afford a yellow solution. Benzoyl chloride (40 µL, 0.34 mmol) was then added to afford a suspension. After stirring for 16 h at ambient temperature, TLC and LC/MS analysis showed starting amine present. The reaction mixture was then heated in a 50°C oil bath. After 3 h at 50°C, TLC and LC/MS analysis showed little progress in the reaction. Additional benzoyl chloride (50 µL, 0.43 mmol) was added to the reaction. After stirring for 26 h after the addition of the second portion of benzoyl chloride the reaction was cooled to ambient temperature, quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), and diluted with ethyl acetate (30 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL), the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 12:1 then 10:1 hexane:ethyl acetate to afford *N*-{4-[2-(1-cyclohexen-1-yl)ethynyl]-1,3-thiazol-2-yl}benzamide (37 mg, 70 %) as an oil that partially solidified under high vacuum. The material was not completely pure by NMR analysis, and was then carefully purified by column chromatography on silica gel eluting with 15:1 then 12:1 hexane:ethyl acetate to afford *N*-{4-[2-(1-cyclohexen-1-yl)ethynyl]-1,3-thiazol-2-

yl}benzamide (30 mg, 57%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, J=7.3 Hz, 2H), 7.58 (t, J=7.3 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.09 (s, 1H), 5.92-5.80 (m, 1H), 2.05-2.00 (m, 2H), 1.95-1.87 (m, 2H), 1.59-1.49 (m, 2H). MS (ESI) 309.1 (M^++H), 331.0 (M^++Na).

Example 169

Synthesis of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

$PdCl_2$ (15 mg, 85 μmol), and CuI (23 mg, 120 μmol) were combined in DME (3 mL) under argon. H_2O (1 mL) was added and argon was bubbled through the resulting dark suspension while it was warmed to 40°C in an oil bath. Triphenylphosphine (84 mg, 320 μmol) was added and the argon flow was continued for 10 min. The argon flow was discontinued, solid potassium carbonate (277 mg, 2.0 mmol) was added, followed by 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (90 mg, 0.46 mmol) and 3-bromopyridine (56 μL, 0.58 mmol) as a solution in DME (2 mL) followed by a rinse of the flask and syringe with DME (1 mL). The temperature was raised to 75°C. After 16 h there was still 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole visible by GC/MS analysis. At this time Bu_4NF (1.0 mL of a 1.0M solution in THF, 1.0 mmol) was added to the reaction mixture. After 10 min GC/MS analysis showed the reaction was complete. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (50 mL), and H_2O (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL), the combined organics were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 2:1, 1:1, then 2:3 hexane:ethyl acetate to afford product contaminated with some close-running impurities. The material was then carefully purified by column chromatography on silica gel eluting with 2:1, then 1:1 hexane:ethyl acetate to afford 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (48.6 mg, 52 %) as a pale brown oil that partially solidified after pumping down under high vacuum. M.p.= 75-76°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.0-8.7 (br s, 1H), 8.7-8.45 (br s, 1H), 7.84 (d, J=7.9 Hz, 1H), 7.45 (s, 1H), 7.35-7.22 (m, 1H), 2.75 (s, 1H). MS (EI ionization) 200 (M^+).

Example 170

Synthesis of 2,4-dimethyl-6-[(trimethylsilyl)ethynyl]pyrimidine

A solution of trifluoromethanesulfonic anhydride (6.5 mL, 39 mmol) was added slowly to a stirred solution of 2,4-dimethyl-6-hydroxypyrimidine (4.0 g, 32 mmol) and triethylamine (7.5 mL, 53 mmol) in dry CH_2Cl_2 (125 mL) at 0°C under argon. The mixture was stirred at ambient temperature for 16 h at which time TLC analysis showed the reaction to be complete. The mixture was diluted with CH_2Cl_2 (200 mL), washed with saturated aqueous $NaHCO_3$ (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Half of the residue (4 g, 16 mmol) was dissolved in DME (10 mL), and argon was bubbled through the solution for several min to deoxygenate it. Trimethylsilylacetylene (2.9 g, 30 mmol) was added. The resulting solution was added to a

deoxygenated mixture of $PdCl_2$ (83 mg, 0.47 mmol), triethylamine (8.7 mL, 1.8 mmol), CuI (259 mg, 1.35 mmol), and triphenylphosphine (483 mg, 1.84 mmol), in DME (20 mL) at 45°C. After stirring for 16 h at 45°C, TLC showed no remaining 2,6-dimethyl-4-pyrimidinyl trifluoromethanesulfonate. The mixture was diluted with ethyl acetate (200 mL), and filtered through Celite™. The filter pad was then thoroughly washed with ethyl acetate and the combined filtrates were washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexane, 20:1, then 9:1 hexane:ethyl acetate to afford 2,4-dimethyl-6-[(trimethylsilyl)ethynyl]pyrimidine (600 mg, 18%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (s, 1H), 2.69 (s, 1H), 2.48 (s, 1H), 0.26 (s, 9H).

Example 171

Synthesis of 4-([1,1'-biphenyl]-4-ylethynyl)-2,6-dimethylpyrimidine

CuI (73 mg, 0.38 mmol), $PdCl_2(PPh_3)_2$ (130 mg, 0.19 mmol), triphenylphosphine (100 mg, 0.38 mmol), and tetrabutylammonium iodide (543 mg, 1.47 mmol) were combined in dry DMF (25 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (1.0 mL, 7.4 mmol), was added, the reaction mixture was warmed to 40°C, and a solution of 4-bromo-1,1'-biphenyl (446 mg, 1.9 mmol) and 2,4-dimethyl-6-[(trimethylsilyl)ethynyl]pyrimidine from Example 170 (300 mg, 1.47 mmol) in DMF (10 mL) was added. The reaction mixture was warmed to 70°C and tetrabutylammonium fluoride (1.9 mL of a 1.0 M solution in THF, 1.3 mmol) was added by syringe pump over 2 h. After stirring for an additional 2 h, TLC and GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (50 mL) and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 18:1, then 9:1 hexane:ethyl acetate to afford 4-([1,1'-biphenyl]-4-ylethynyl)-2,6-dimethylpyrimidine (12 mg, 3%) as a yellow solid. M.p.= 145-148°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.60 (m, 5H), 7.49-7.36 (m, 4H), 7.19 (s, 1H), 2.73 (s, 3H), 2.52 (s, 3H). MS (ESI) 285.0 (M+H).

Example 172

Synthesis of 2-[(trimethylsilyl)ethynyl]pyrazine

$PdCl_2$ (60 mg, 0.34 mmol), CuI (151 mg, 0.79 mmol), and triethylamine (3.8 mL, 27 mmol) were combined in DME (10 mL) under argon. Argon was bubbled through the suspension, and after 10 min triphenylphosphine (349 mg, 1.33 mmol) was added and the reaction flask was immersed in a 50°C oil bath. The argon flow was discontinued after an additional 5 min, then trimethylsilylacetylene (2.4 mL, 17 mmol), and 2-iodopyrazine (1.66 g, 8.06 mmol) were added as a solution in DME (5 mL), followed by a rinse of the flask and syringe with DME (3 mL). After stirring for 16 h at 50°C, GC/MS analysis of the dark brown suspension showed no 2-iodopyrazine remaining. The reaction mixture was

cooled to ambient temperature, filtered, and the solids were washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* to afford a dark oil, which was diluted with diethylether (100 mL), and washed with saturated aqueous $NaHCO_3$ (25 mL). The basic organic layer was extracted with diethylether (50 mL), and the combined organics were washed with brine (25 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, then diluted with benzene and concentrated *in vacuo* again to remove any remaining H_2O as its azeotrope. The crude material was purified by column chromatography on silica gel eluting with hexane, 30:1, then 20:1 hexane:ethyl acetate to afford 2-[(trimethylsilyl)ethynyl]pyrazine (1.2 g, 88%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.89 (s, 1H), 8.55 (d, J=3 Hz, 1H), 8.49 (d, J=3 Hz, 1H), 0.29 (s, 9H). MS (EI ionization) 176 (M^+).

Example 173

Synthesis of 2-([1,1'-biphenyl]-4-ylethynyl)pyrazine

CuI (84 mg, 0.44 mmol), $PdCl_2(PPh_3)_2$ (155 mg, 0.22 mmol), triphenylphosphine (116 mg, 0.442 mmol), and tetrabutylammonium iodide (630 mg, 1.7 mmol) were combined in dry DMF (25 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (0.8 mL, 8 mmol), was added, the reaction mixture was warmed to 40°C, and a solution of 4-bromo-1,1'-biphenyl (515 mg, 2.2 mmol) and 2-[(trimethylsilyl)ethynyl]pyrazine from Example 172 (300 mg, 1.7 mmol) in DMF (10 mL) was added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (2.2 mL of a 1.0 M solution in THF, 2.2 mmol) was added by syringe pump over 2 h. After stirring for an additional 2 h, TLC and GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (50 mL) and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 18:1, 9:1, then 8.5:1.5 hexane:ethyl acetate to afford 2-([1,1'-biphenyl]-4-ylethynyl)pyrazine (100 mg, 23%) as a yellow solid. M.p.= 112-113°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.88 (s, 1H), 8.78 (s, 1H), 8.64 (s, 1H), 7.62-7.61 (m, 6H), 7.50-7.38 (m, 3H). MS (ESI) 257.0 (M+H).

Example 174

Synthesis of 4,6-dimethyl-2-[(trimethylsilyl)ethynyl]pyrimidine

$PdCl_2$ (234 mg, 1.32 mmol), CuI (737 mg, 3.87 mmol), and triethylamine (23 mL, 165 mmol) were combined in DME (50 mL) under argon. Argon was bubbled through the suspension, and after 10 min triphenylphosphine (1.37 g, 5.22 mmol) was added and the reaction flask was immersed in a 50°C oil bath. The argon flow was discontinued after an additional 5 min, then trimethylsilylacetylene (12 mL, 85 mmol), and 4,6-dimethyl-2-pyrimidinyl trifluoromethanesulfonate (11.3 g, 44.1 mmol), were added as a solution in DME (10 mL) followed by a rinse of the flask and syringe with DME (10 mL). The reaction mixture rapidly turned from a dark orange color to black as the 4,6-dimethyl-2-

pyrimidinyl trifluoromethanesulfonate solution was added. After stirring for 30 min at 50°C, GC/MS analysis of the black suspension showed no 4,6-dimethyl-2-pyrimidinyl trifluoromethanesulfonate remaining. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo*, diluted with diethylether (200 mL), filtered, and the solids were washed thoroughly with diethylether. The combined filtrates were washed with saturated aqueous $NaHCO_3$ (50 mL), at which time a large quantity of solids appeared. The suspension was again filtered. The two layers of the filtrate were separated, and the aqueous layer was extracted with diethylether (2 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel eluting with hexane, 20:1, 10:1, then 8:1 hexane:ethyl acetate to afford an orange oil with some white fluffy solids present. This was diluted with hexane and filtered through a plug of Celite™ to remove the white solids. The filtrate was concentrated *in vacuo* to afford 4,6-dimethyl-2-[(trimethylsilyl)ethynyl]pyrimidine (4.63 g, 51%) as an orange oil. During the elution of the column, while the desired compound was eluting, the flow rate dropped and the column plugged so that elution was no longer possible. The silica gel from the column was slurried with ethyl acetate and CH_2Cl_2, and filtered. The silica gel was then washed thoroughly with ethyl acetate. The combined filtrates were combined and concentrated *in vacuo* to afford a dark oil, which was quite clean by NMR analysis showing desired product contaminated with some material exhibiting extra phenyl signals (possibly triphenylphosphine). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1H), 2.49 (s, 3H), 0.28 (s, 9H). MS (EI ionization) 204 (M^+).

Example 175

Synthesis of 2-([1,1'-biphenyl]-4-ylethynyl)-4,6-dimethylpyrimidine

CuI (84.0 mg, 0.442 mmol), $PdCl_2(PPh_3)_2$ (155 mg, 0.22 mmol), triphenylphosphine (116 mg, 0.44 mmol), and tetrabutylammonium iodide (630 mg, 1.7 mmol) were combined in dry DMF (25 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (0.8 mL, 8 mmol), was added, the reaction mixture was warmed to 40°C, and a solution of 4-bromo-1,1'-biphenyl (515 mg, 2.2 mmol) and 4,6-dimethyl-2-[(trimethylsilyl)ethynyl]pyrimidine from Example 174 (340 mg, 1.7 mmol) in DMF (10 mL) was added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (2.2 mL of a 1.0 M solution in THF, 2.2 mmol) was added by syringe pump over 2 h. After stirring for an additional 2 h, TLC and GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (50 mL) and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 18:1, 9:1, 8.5:1.5 hexane:ethyl acetate to afford 2-([1,1'-biphenyl]-4-ylethynyl)-4,6-dimethylpyrimidine (180 mg, 42%) as a yellow solid. The 2-([1,1'-biphenyl]-4-ylethynyl)-4,6-dimethylpyrimidine was dissolved in diethylether (20 mL) and HCl (12 mL of a 1.0 M solution in diethylether, 12 mmol) was added. The resulting

precipitate was filtered, and crystallized from boiling ethyl acetate to afford 2-([1,1'-biphenyl]-4-ylethynyl)-4,6-dimethylpyrimidine hydrochloride (50 mg , 11%) as yellow crystals. M.p.= 163-165°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, J=3 Hz, 4H), 7.72-7.67 (m, 3H), 7.51-7.41 (m, 3H), 2.70(s, 6H). MS (ESI) 285.1 (M+H).

Example 176

Synthesis of 1-chloro-6-(trimethylsilyl)-3,5-hexadiyn-2-one

Aluminum trichloride (6.85 g, 51.4 mmol) was suspended in CH_2Cl_2 (100 mL) and cooled in an ice bath. A solution of 4-bis(trimethylsilyl)1,3-butadiyne (10.0 g, 51.4 mmol) and chloroacetyl chloride (4.1 mL, 51 mmol) in CH_2Cl_2 (100 mL) was added to the $AlCl_3$ suspension dropwise from an addition funnel over 1 h. The dark brownish-red solution was stirred at 0°C for 1 h, then the ice bath was removed. After 1 h at ambient temperature, the reaction was cooled to 0°C and quenched by slow addition of 1M HCl (150 mL). The acidic aqueous solution was extracted with CH_2Cl_2 (2 x 300 mL), the combined organic layers were washed with H_2O (500 mL), saturated aqueous $NaHCO_3$ (500 mL), brine (500 mL) and dried over Na_2SO_4. The organic layer was filtered to afford a clear solution which was concentrated *in vacuo*. The crude 1-chloro-6-(trimethylsilyl)-3,5-hexadiyn-2-one (10 g) was used in the next step without purification. MS (EI ionization) 183 (M^+).

Example 177

Synthesis of 2-methyl-4-[4-(trimethylsilyl)-1,3-butadiynyl]-1,3-thiazole

Crude 1-chloro-6-(trimethylsilyl)-3,5-hexadiyn-2-one from Example 176 (5.0 g, 25 mmol) was dissolved in DMF (70 mL), then thioacetamide (2.4 g, 33 mmol) was added in one portion. The mixture was allowed to stir for 16 h at ambient temperature, at which time TLC showed no remaining 1-chloro-6-(trimethylsilyl)-3,5-hexadiyn-2-one. The mixture was diluted with ethyl acetate (200 mL), washed with H_2O (3 x 300 mL), brine (300 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexane, then 20:1 hexane:ethyl acetate to afford 2-methyl-4-[4-(trimethylsilyl)-1,3-butadiynyl]-1,3-thiazole (1.2 g, 24%) as reddish-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 1H), 2.68 (s, 3H), 0.26 (s, 9H). MS (EI ionization)219 (M^+).

Example 178

Synthesis of N-hydroxybenzenecarboximidoyl chloride

To a solution of *syn*-benzaldehyde oxime (12 g, 99 mmol) in DMF (70 mL) was added N-chlorosuccinimide (15.8 g, 118 mmol). After stirring at ambient temperature for 64 h, TLC analysis showed no starting oxime present. The reaction mixture was diluted with diethylether (600 mL), washed with a 1:1 mixture of H_2O:saturated aqueous NaCl (2 x 200 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford an oil that was diluted with toluene and concentrated *in vacuo* to remove any remaining H_2O. The resulting crude product was purified by

column chromatography on silica gel eluting with hexane, 30:1, then 20:1 hexane:ethyl acetate to afford N-hydroxybenzenecarboximidoyl chloride (5.77 g, 37%) as white crystals. M.p.= 52-53°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.00 (s, 1H), 7.84 (d, J=6 Hz, 2H), 7.49-7.37 (m, 3H).

Example 179

Synthesis of 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-phenylisoxazole

To a solution of 2-methyl-4-[4-(trimethylsilyl)-1,3-butadiynyl]-1,3-thiazole from Example 177 (220 mg, 1.0 mmol) in dry diethylether (20 mL) under argon, tetrabutylammonium fluoride (1.1 mL of a 1.0 M solution in THF, 1.1 mmol) was added by syringe during 15 min. After stirring for 0.5 h, TLC and GC/MS analysis showed the reaction to be complete. Then N-hydroxybenzenecarboximidoyl chloride from Example 178 (233 mg, 1.5 mmol) was added in one portion under argon. Triethylamine (0.20 mL in 20 mL dry diethylether, 1.5 mmol) was added by addition funnel during 2 h. After stirring for an additional 2 h, TLC and GC/MS analysis showed the reaction was not complete, another 1.5 mmol of N-hydroxybenzenecarboximidoyl chloride and triethylamine was added as described above. After stirring for an additional 2h, the mixture was diluted with diethylether (50 mL) and washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 18:1, then 9:1 hexane:ethyl acetate to afford 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-phenylisoxazole (195 mg, 73%) as a yellow solid. The product was dissolved in diethylether (20 mL) and HCl (15 mL of a 1.0 M solution in diethylether, 15 mmol) was added, the resulting precipitate was filtered and washed with diethylether to give 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-phenylisoxazole (90 mg , 34%) as yellow crystals. M.p.= 118-120°C. Elemental analysis of the material for C, H, N and Cl showed the material to be the free base, not the hydrochloride salt. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (s, 1H), 7.88-7.84 (m, 2H), 7.50-7.47 (m, 3H), 7.21 (s, 1H), 2.73 (s, 3H). MS (ESI) 267.0 (M+H).

Example 180

Synthesis of Ethyl 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-isoxazolecarboxylate

To a solution of 2-methyl-4-[4-(trimethylsilyl)-1,3-butadiynyl]-1,3-thiazole from Example 177 (150 mg, 0.68 mmol) in dry diethylether (20 mL) under argon, tetrabutylammonium fluoride (0.75 mL of a 1.0 M solution in THF, 0.75 mmol) was added by syringe during 15 min. After stirring for 0.5 h, TLC and GC/MS analysis showed the reaction to be complete. Then commercially available ethyl (2-*E,Z*)-chloro(hydroxyimino)ethanoate (155 mg, 1.0 mmol) was then added in one portion under argon. Triethylamine (0.14 mL, 1.0 mmol) was added as a solution in dry diethylether (20 mL) by addition funnel during 2 h. After stirring for an additional 2 h, TLC and GC/MS analysis showed the reaction was not complete. Another portion of ethyl (2-*E,Z*)-chloro(hydroxyimino)ethanoate (155 mg, 1.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) was added as described above. After stirring for an additional 2 h, the mixture was diluted with diethylether (50 mL) and washed with H_2O (100 mL), brine

(100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 18:1, then 9:1 hexane:ethyl acetate to afford ethyl 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-isoxazolecarboxylate (120 mg, 72%) as a yellow solid. The ethyl 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-isoxazolecarboxylate was dissolved in diethylether (20 mL) and HCl (16 mL of a 1.0 M solution in diethylether, 16 mmol) was added. The resulting precipitate was filtered and washed with diethylether to give ethyl 5-[(2-methyl-1,3-thiazol-4-yl)-ethynyl]-3-isoxazolecarboxylate (75 mg, 42%) as yellow crystals. M.p.= 125-127°C. Elemental analysis for C, H, N, and Cl showed the compound to be the free base, not the hydrochloride salt. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 7.21 (s, 1H), 4.43 (q, J=9 Hz, 2H), 2.87 (s, 3H), 1.40(t, J=6 Hz, 3H). MS (ESI) 263.0 (M+H).

Example 181

Synthesis of 2-methoxy-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

CuI (40 mg, 0.2 mmol), $PdCl_2(PPh_3)_2$ (72 mg, 0.10 mmol), triphenylphosphine (54 mg, 0.2 mmol), and tetrabutylammonium iodide (376 mg, 1.0 mmol) were combined in dry DMF (20 mL) and argon gas was bubbled through the mixture for several min to deoxygenate it. Triethylamine (0.71 mL, 5.1 mmol) was added, the reaction mixture was warmed to 40°C, and a solution of 5-bromo-2-methoxypyridine (231 mg, 1.23 mmol) and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (200 mg, 1.0 mmol) in DMF (10 mL) was added. The reaction was warmed to 70°C and tetrabutylammonium fluoride (1.3 mL of a 1.0 M solution in THF, 1.3 mmol) was added by syringe pump over 2 h. After stirring for an additional 2 h, TLC and GC/MS analysis showed the reaction to be complete. The mixture was diluted with ethyl acetate (100 mL) and filtered through Celite™. The filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were washed with H_2O (2 x 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane, 18:1, then 9:1 hexane:ethyl acetate to afford 2-methoxy-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (150 mg, 20%) as a yellow solid. The product was further purified by crystallization from boiling hexane to give 2-methoxy-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (120 mg, 51%) as yellow crystals. M.p.= 110-111°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (d, J=2 Hz, 1H), 7.71 (dd, J=2, 9 Hz, 1H), 7.37 (s, 1H), 6.73 (d, J=9 Hz, 1H). MS (ESI) 230.9 (M+H).

Example 182

Synthesis of 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyrimidine

$PdCl_2$ (27.8 mg, 160 μmol), CuI (77 mg, 400 μmol), and triethylamine (3.0 mL, 22 mmol) were combined in DME (10 mL) under argon. Argon was bubbled through the suspension, and after 10 min triphenylphosphine (166 mg, 630 μmol) was added and the reaction flask was heated on a heating mantle. The argon flow was discontinued after an additional 5 min, then 5-bromopyrimidine (830 mg,

5.2 mmol), and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (826 mg, 4.2 mmol), were added as a solution in DME (5 mL) followed by a rinse of the flask and syringe with DME (2 mL). Tetrabutylammonium fluoride (5.0 mL of a 1.0 M solution in THF, 5.0 mmol) was then added to the reaction mixture dropwise over 10 min. After stirring for an additional 2.5 h at 65°C, GC/MS analysis showed no remaining 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole, nor desilylated alkyne present. The reaction mixture was allowed to slowly cool to ambient temperature over 16 h, concentrated *in vacuo*, diluted with ethyl acetate (150 mL), H_2O (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The basic aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford a brown solid. The crude product was purified by column chromatography on silica gel eluting with hexane 3:1, 2:1, then 3:2 hexane:ethyl acetate to afford 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyrimidine (687 mg, 81 %) as a brownish-yellow solid. M.p. 118.5-119.5°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.17 (s, 1H), 8.89 (s, 2H), 7.51 (s, 1H), 2.76 (s, 3H). MS (EI ionization) 201 (M^+).

Example 183

Synthesis of 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]nicotinonitrile

$PdCl_2$ (25 mg, 140 mol), CuI (78 mg, 410 mol), and triethylamine (3.0 mL, 22 mmol) were combined in DME (10 mL) under argon. Argon was bubbled through the suspension, and after 10 min triphenylphosphine (150 mg, 570 mol) was added and the reaction flask was heated on a heating mantle. The argon flow was discontinued after an additional 5 min, then 5-bromonicotinonitrile (980 mg, 5.3 mmol), and 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole from Example 77 (867 mg, 4.4 mmol), were added as a solution in DME (5 mL) followed by a rinse of the flask and syringe with DME (2 mL). Tetrabutylammonium fluoride (5.0 mL of a 1.0 M solution in THF, 5.0 mmol) was then added to the reaction mixture dropwise over 10 min. After stirring for 16 h at 55°C, GC/MS analysis showed no remaining 2-methyl-4-[(trimethylsilyl)ethynyl]-1,3-thiazole, nor desilylated alkyne present. The reaction mixture was allowed to cool to ambient temperature overnight, concentrated *in vacuo*, diluted with ethyl acetate (150 mL), H_2O (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The basic aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford a brown solid. The crude product was purified on a Biotage Flash system eluting with 100:1 $CHCl_3$:CH_3OH to afford 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]nicotinonitrile (201 mg, 20 %) as a yellow solid. (there were a large number of impure fractions from the column) M.p. 173-175°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.94 (d, J=2.0 Hz, 1H), 8.82 (d, J=2.0 Hz, 1H), 8.08 (t, J=2.0 Hz, 1H), 7.52 (s, 1H), 2.77 (s, 3H). MS (EI ionization) 225 (M^+).

Example 184

Calcium Flux Assay

The activity of compounds was examined against the hmGluR5a receptor stably expressed in mouse fibroblast Ltk⁻ cells (the hmGluR5a/L38-20 cell line). See generally Daggett *et al.*, *Neuropharmacology* 34:871-886 (1995). Receptor activity was detected by changes in intracellular calcium ($[Ca^{++}]_i$) measured using the fluorescent calcium-sensitive dye, fura-2. hmGluR5a/L38-20 cells were plated onto 96-well plates, and loaded with 3 μM fura-2 for 1 h. Unincorporated dye was washed from the cells, and the cell plate was transferred to a custom-built 96-channel fluorimeter (SIBIA-SAIC, La Jolla, CA) which is integrated into a fully automated plate handling and liquid delivery system. Cells were excited at 350 and 385 nm with a xenon source combined with optical filters. Emitted light was collected from the sample through a dichroic mirror and a 510-nm interference filter and directed into a cooled CCD camera (Princeton Instruments). Image pairs were captured approximately every 1 s, and ratio images were generated after background subtraction. After a basal reading of 20 s, an EC_{80} concentration of glutamate (10 μM) was added to the well, and the response evaluated for another 60 s. The glutamate-evoked increase in $[Ca^{++}]_i$ in the presence of the screening compound was compared to the response of glutamate alone (the positive control). Results obtained from testing certain exemplary compounds from this assay are presented in Table 1.

Example 185

Phosphatidylinositol hydrolysis (IP1) assays

Inositol phophate assays were performed as described by Berridge *et al.* (1982) (Berridge *et al,* (1982) *Biochem. J.* 206: 587-5950; and Nakajima *et al., J Biol. Chem.* 267:2437-2442 (1992)) with slight modifications. Mouse fibroblast Ltk cells expressing hmGluR5 (hmGluR5/L38-20 cells) were seeded in 24-well plates at a density of $8x10^5$ cells/well. One μCi of [^{3}H]-inositol (Amersham PT6-271; Arlington Heights, Ill.; specific activity = 17.7 Ci/mmol) was added to each well and incubated for 16 h at 37°C. Cells were washed twice and incubated for 45 min in 0.5 ml of standard Hepes buffered saline buffer (HBS; 125 mM NaCl, 5 mM KCl, 0.62 mM $MgSO_4$, 1.8 mM $CaCl_2$, 20 mM HEPES, 6 mM glucose, pH to 7.4). The cells were washed with HBS containing 10 mM LiCl, and 400 μl buffer added to each well. Cells were incubated at 37°C for 20 min. For testing, 50 μl of 10X compounds used in the practice of the invention (made in HBS/LiCl (100 mM)) was added and incubated for 10 minutes. Cells were activated by the addition of 10 μM glutamate, and the plates left for 1 hour at 37°C.

The incubations were terminated by the addition of 1 ml ice-cold methanol to each well. In order to isolate inositol phosphates (IPs), the cells were scraped from wells, and placed in numbered glass test tubes. One ml of chloroform was added to each tube, the tubes were mixed, and the phases separated by centrifugation. IPs were separated on Dowex anion exchange columns (AG 1-X8 100-200 mesh formate form). The upper aqueous layer (750 ul) was added to the Dowex columns, and the

columns eluted with 3 ml of distilled water. The eluents were discarded, and the columns were washed with 10 mls of 60 mM ammonium formate/5 mM Borax, which was also discarded as waste. Finally the columns were eluted with 4 ml of 800 mM ammonium formate/0.1 M formic acid, and the samples collected in scintillation vials. Scintillant was added to each vial, and the vials shaken, and counted in a scintillation counter after 2 hours. Phosphatidylinositol hydrolysis in cells treated with certain exemplary compounds was compared to phosphatidylinositol hydrolysis in cells treated with control and the results are shown in Table 1.

Example 186

Analgesic Animal Model (CFA Model)

Compounds that modulate receptor-mediated analgesic responses were tested in an animal model. Robust inflammation was induced by the injection of complete Freund's adjuvant (CFA, 10 mg/ml) subcutaneously into the hind paw of male Sprague-Dawley rats (150-175 g). The inflammatory response to CFA began approximately 12-hrs post-CFA injection and persisted for several days following inoculation. The inflamed hind paw became sensitive to noxious (paw pinch, plantar test) or innocuous (cold plate, Von Frey filaments) stimuli compared to the contralateral hind paw. Test compounds (240 µmol/kg) were administered via intraperitoneal injection. The analgesic activity of compounds was evaluated one to 24-hours post administration by assessing (1) the duration of analgesic effect; (2) threshold to elicit response; and (3) time from painful stimulus to response. A general increase in duration of analgesic effect, threshold to painful stimuli or time to respond following compound administration suggested analgesic efficacy. For each group of animals, responses following administration of certain exemplary compounds were compared to responses prior to compound administration. Results are presented in Table 1.

TABLE 1*

Example	Ca^{2+} Flux	PI Hydrolysis	CFA Model
44	+	-	ND
45	+	-	ND
46	+	+	+
47	+	+	+
48	+	+	ND
49	+	-	-
50	+	-	ND
51	+	+	+
52	+	+	ND
53	-	-	ND
54	+	+	+
55	+	+	ND
56	+	+	ND
57	+	+	ND
58	-	-	ND
59	-	-	ND
60	-	-	ND
61	-	-	ND

62	+	-	ND
63	+	-	ND
64	-	-	ND
65	+	+	-
66	+	+	ND
67	ND	-	ND
69	+	+	ND
74	ND	-	ND
75	+	+	ND
79	+	+	+
80	+	+	+
82	+	+	ND
83	+	-	ND
86	+	+	+
87	+	+	ND
88	+	+	ND
89	+	+	+
90	+	+	ND
91	+	ND	ND
92	+	+	ND
93	+	+	ND
94	ND	-	ND
95	+	+	-
96	+	+	ND
98	+	+	ND
100	+	ND	ND
101	+	+	+
103	-	ND	ND
104	+	+	ND
105	+	+	ND
106	+	+	ND
107	+	+	ND
108	+	+	-
109	+	+	ND
110	+	+	+
111	+	+	+
112	+	+	+
113	+	+	-

114	+	+	ND
115	+	+	ND
117	+	+	ND
118	+	+	ND
120	+	+	+
124	ND	-	ND
126	+	+	ND
127	+	+	ND
131	+	+	ND
133	+	+	+
134	+	+	ND
135	+	+	-
136	+	+	ND
137	+	+	ND
138	+	+	ND
139	+	+	ND
140	+	ND	ND
141	+	+	ND
142	+	+	ND
143	+	+	ND
144	+	+	ND
145	+	+	ND
148	ND	+	ND
150	+	+	-
152	+	+	ND
155	+	+	ND
157	+	+	+
158	+	+	ND
159	+	+	ND
160	+	+	ND
161	+	+	ND
162	+	+	ND
163	+	+	ND
164	+	+	ND
165	+	+	ND
166	+	+	-
167	+	+	ND
168	+	-	ND

169	+	+	+
173	+	+	ND
179	+	+	-
180	+	+	ND

181	+	ND	ND
182	+	+	ND
183	+	+	+

***Table Legend:**

Ca^{2+} Flux:

+: 0.1 nmol $\leq IC_{50} \leq$ 10 μmol

-: IC_{50} > 10 μmol

PI Hydrolysis:

+: 1.0 nmol $\leq IC_{50} \leq$ 10 μmol

-: IC_{50} > 10 μmol

CFA Model:

+ = analgesic efficacy

- = analgesic inefficacy

ND = not determined

Data presented in Table 1 demonstrate that the activity of metabotropic glutamate receptor 5 (mGluR5), assessed by measuring receptor-activated changes in calcium flux, may be modulated by compounds contemplated for use in the practice of the invention. In assays using cells transfected with mGluR5a, a majority of invention compounds are effective at decreasing intracellular calcium flux, and decreasing phosphoinositol hydrolysis.

Example 187

Salt forms of 2-(Phenylethynyl)-1,3-thiazole

Various salt forms of 2-(phenylethynyl)-1,3-thiazole were prepared, and their solubility, hygroscopicity, and physical state were assessed. The compound 2-phenylethynl-1,3-thiazole was prepared (see Example 8) as well as hydrochloric acid, fumaric acid, methylsulfonic acid and toluene sulfonic acid salt forms of the compound. The hydrochloric acid salt form of 2-(phenylethynyl)-1,3-thiazole is an oil. A fumaric acid salt form was not obtained by preparative steps including trituration with diethylether. Preparation of the methylsulfonate form results in a semi solid, hygroscopic material. These salt forms are typically unsuitable for certain pharmaceutical formulations, such as for tablets, capsules, and the like. In contrast to the salt forms of 2-(phenylethynyl)-1,3-thiazole, described previously, the tosylate salt form (*i.e.*, the toluene sulfonic acid salt) is a solid having a melting point of about 129 up to 131°C and is non-hygroscopic. Therefore, this form is presently preferred for pharmaceutical formulations of tablets, capsules, and the like.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

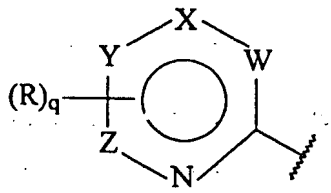
WHAT IS CLAIMED IS:

1. A compound having the structure:

A — L — B

or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein:

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of **W, X, Y** and **Z** is $(CR)_p$, wherein p is 0, 1 or 2;

the remainder of W, X, Y and Z are each independently O, N or S; and

each R is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded:

the compounds wherein **A** is a 6-membered ring wherein:

W, X, Y and **Z** are $(CR)_p$ wherein p is 1; and

R at the W position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at the X position is hydrogen; R at the Y position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Z position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy,

unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo; and

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents; and

the compounds wherein **A** is a 6-membered ring wherein:

W, X, Y and **Z** are $(CR)_p$ wherein p is 1; R at the X position is not hydrogen; and R at the W, Y and Z positions are hydrogen;

L is alkenylene or alkynylene; and

B is a substituted or unsubstituted aryl or heterocycle containing two or more double bonds; and

the compounds wherein **A** is a 5-membered ring wherein:

one of **W, X, Y** and **Z** is $(CR)_p$, and p is 0, two of **W, X, Y** and **Z** are $(CR)_p$ and p is 1, and the remaining variable ring member is O or S; or

one of **W, X, Y** and **Z** is N, one of **W, X, Y** and **Z** is $(CR)_p$ and p is 1, one of **W, X, Y** and **Z** is $(CR)_p$ and p is 0, and the remaining variable ring member is O, S or $(CR)_p$, and p is 1; or

two of **W, X, Y** and **Z** are N, one of **W, X, Y** and **Z** is $(CR)_p$, and p is 0, and the remaining variable ring member is , O or S or $(CR)_p$, and p is 1;

each R is independently hydrogen, nitro, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, C_1-C_4-haloalkylthio, C_3-C_6-alkenyl or C_3-C_8-cycloalkyl;

L is alkynylene; and

B is substituted or unsubstituted aryl, wherein substituents are independently nitro, cyano, C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkthio, C_1-C_4-haloalkylthio, C_1-C_4-alkoxycarbonyl, C_3-C_6-alkenyl, phenyl or phenoxy, wherein phenyl and phenoxy may bear further substituents; and

the compounds wherein **A** is a 6-membered ring wherein:

W, X, Y and **Z** are (CR)p, wherein p is 1 and R is hydrogen,

L is alkynylene; and

B is unsubstituted 1-cyclopenten-1-yl or unsubstituted 1-cyclohexen-1-yl; and

the compounds wherein **A** is a 5-membered ring wherein:

W is (CR)p, and p is 0, **Y** and **Z** are (CR)p, and p is 1, **X** is N or S; and **R** is phenyl; or

W is (CR)p, and p is 0, **X and Z** are (CR)p, and p is 1, **Y** is O, N or S; and R is phenyl;

L is unsubstituted alkenylene and

B is unsubstituted phenyl; and

the compounds wherein **A** is a 5-membered ring containing two double bonds, wherein one of **W, X, Y** and **Z** is $(CR)_p$, and p is 0, and the remaining ring members are $(CR)_p$ and p is 1; and

the compounds wherein **A** is unsubstituted heterocycle containing two or more double bonds; **L** is alkenylene or alkynylene, and **B** is unsubstituted phenyl.

2. A compound according to claim 1, wherein one of W, X, Y, and Z is S; and the remainder of W, X, Y and Z are $(CR)_p$.

3. A compound according to claim 2, wherein L is substituted or unsubstituted alkenylene.

4. A compound according to claim 3, wherein one of W, X, Y, and Z is S; one of W, X, Y and Z is (CR)p, wherein p is 0 and the remainder of W, X, Y and Z is (CR)p, wherein p is 1.

5. A compound according to claim 2, wherein L is alkynylene.

6. A compound according to claim 5, wherein one of W, X, Y, and Z is S; one of W, X, Y and Z is (CR)p, wherein p is 0 and the remainder of W, X, Y and Z is (CR)p, wherein p is 1.

7. A compound according to claim 1, wherein one of W, X, Y and Z is O, and the remainder of W, X, Y and Z are (CR)p.

8. A compound according to claim 7, wherein L is substituted or unsubstituted alkenylene.

9. A compound according to claim 8, wherein one of W, X, Y and Z is O, one of W, X, Y and Z is (CR)p, wherein p is 0 and the remainder of W, X, Y and Z is (CR)p, wherein p is 1.

10. A compound according to claim 7, wherein L is alkynylene.

11. A compound according to claim 10, wherein one of W, X, Y and Z is O, one of W, X, Y and Z is (CR)p, wherein p is 0 and the remainder of W, X, Y and Z is (CR)p, wherein p is 1.

12. A compound according to claim 1, wherein one of W, X, Y and Z is N, and the remainder of W, X, Y and Z is (CR)p.

13. A compound according to claim 12, wherein L is substituted or unsubstituted alkenylene.

14. A compound according to claim 13, wherein one of W, X, Y and Z is N, and the remainder of W, X, Y and Z is (CR)p, wherein p is 1.

15. A compound according to claim 12, wherein L is alkynylene.

16. A compound according to claim 15, wherein one of W, X, Y and Z is N, and the remainder of W, X, Y and Z is (CR)p, wherein p is 1.

17. A compound according to claim 1, wherein two of W, X, Y and Z are N, and the remainder of W, X, Y and Z are (CR)p.

18. A compound according to claim 17, wherein L is substituted or unsubstituted alkenylene.

19. A compound according to claim 18, wherein two of W, X, Y and Z are N, one of W, X, Y and Z is (CR)p, and p is 0 and the remaining ring member is (CR)p, wherein p is 1.

20. A compound according to claim 18, wherein two of W, X, Y and Z are N, and the remaining ring members are (CR)p, wherein p is 1.

21. A compound according to claim 17, wherein L is alkynylene.

22. A compound according to claim 21, wherein two of W, X, Y and Z are N, one of W, X, Y and Z is (CR)p, and p is 0 and the remaining ring member is (CR)p, wherein p is 1.

23. A compound according to claim 21, wherein two of W, X, Y and Z are N, and the remaining ring members are (CR)p, wherein p is 1.

24. A compound according to claim 1, wherein three of W, X, Y and Z are N, and the ring member which is not N, is (CR)p.

25. A compound according to claim 24, wherein L is substituted or unsubstituted alkenylene.

26. A compound according to claim 24, wherein L is alkynylene.

27. A compound according to claim 1, wherein W, X, Y and Z are (CR)p.

28. A compound according to claim 27, wherein L is alkenylene.

29. A compound according to claim 28, wherein W, X, Y and Z are (CR)p, wherein p is 1.

30. A compound according to claim 27, wherein L is alkynylene.

31. A compound according to claim 30, wherein W, X, Y and Z are (CR)p, wherein p is 1.

32. A compound according to claim 1, wherein one of W, X, Y and Z is N, one of W, X, Y and Z is S, and the remainder of W, X, Y and Z are (CR)p.

33. A compound according to claim 32, wherein L is substituted or unsubstituted alkenylene.

34. A compound according to claim 33, wherein one of W, X, Y and Z is N, one of W, X, Y and Z is S, one of W, X, Y and Z is (CR)p, wherein p is 0 and the remaining ring member is (CR)p, wherein p is 1.

35. A compound according to claim 32, wherein L is alkynylene.

36. A compound according to claim 35, wherein one of W, X, Y and Z is N, one of W, X, Y and Z is S, one of W, X, Y and Z is (CR)p, wherein p is 0 and the remaining ring member is (CR)p, wherein p is 1.

37. A compound according to claim 1, wherein one of W, X, Y, and Z is N, one of W, X, Y and Z is O, and the remainder of W, X, Y and Z are (CR)p.

38. A compound according to claim 37, wherein L is substituted or unsubstituted alkenylene.

39. A compound according to claim 38, wherein one of W, X, Y, and Z is N, one of W, X, Y and Z is O, one of W, X, Y and Z is (CR)p, wherein p is 0 and the remaining ring member is (CR)p, wherein p is 1.

40. A compound according to claim 37, wherein L is alkynylene.

41. A compound according to claim 40, wherein one of W, X, Y, and Z is N, one of W, X, Y and Z is O, one of W, X, Y and Z is (CR)p, wherein p is 0 and the remaining ring member is (CR)p, wherein p is 1.

42. A compound according to claim 1, wherein L is an azo group.

43. A compound according to claim 1, wherein L is alkenylene.

44. A compound according to claim 1, wherein L is alkynylene.

45. A compound according to claim 1, wherein B is substituted or unsubstituted hydrocarbyl.

46. A compound according to claim 45, wherein L is alkenylene.

47. A compound according to claim 45, wherein L is alkynylene.

48. A compound according to claim 1, wherein B is cyclohydrocarbyl.

49. A compound according to claim 48, wherein L is alkenylene.

50. A compound according to claim 48, wherein L is alkynylene.

51. A compound according to claim 1, wherein B is substituted or unsubstituted aryl.

52. A compound according to claim 51, wherein L is alkenylene.

53. A compound according to claim 51, wherein L is alkynylene.

54. A compound according to claim 1, wherein B is substituted or unsubstituted heterocycle optionally containing one or more double bonds.

55. A compound according to claim 54, wherein L is alkenylene.

56. A compound according to claim 55, wherein B is substituted or unsubstituted heterocycle containing no double bonds or one double bond.

57. A compound according to claim 54, wherein L is alkynylene.

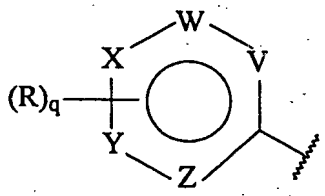
58. A compound according to claim 57, wherein B is substituted or unsubstituted heterocycle containing no double bonds or one double bond.

59. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier therefor.

60. A method of modulating the activity of excitatory amino acid receptors, said method comprising:

contacting said receptors with at least one compound having the structure **A — L — B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, in an amount sufficient to modulate the activity of said excitatory amino acid receptor, wherein :

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of **V, W, X, Y and Z** is $(CR)_p$, wherein p is 0, 1 or 2;

at least one of **V, W, X, Y and Z** is O, N or S;

the remainder of **V, W, X, Y and Z** are each independently O, N or S; and

each **R** is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded:

the compounds wherein **A** is a 6-membered ring wherein:

V, **W**, **X** and **Y** are $(CR)_p$, wherein p is 1;

Z is N;

R at the V position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at the W position is hydrogen; R at the X position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Y position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo, and

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents.

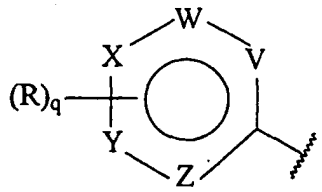
61. A method according to claim 60, wherein said excitatory amino acid receptor is a metabotropic glutamate receptor.

62. A method according to claim 61, wherein said metabotropic glutamate receptor is a Group I metabotropic glutamate receptor.

63. A method for treating disease conditions, said method comprising:

administering to a patient having a disease condition a therapeutically effective amount of at least one compound having the structure **A — L — B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein :

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of **V, W, X, Y and Z** is $(CR)_p$, wherein p is 0, 1 or 2;

at least one of **V, W, X, Y and Z** is O, N or S;

the remainder of **V, W, X, Y and Z** are each independently O, N or S; and

each **R** is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded: the compounds wherein **A** is a 6-membered ring wherein:

V, W, X and **Y** are $(CR)_p$, wherein p is 1;

Z is N;

R at the V position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at the W position is hydrogen; R at the X position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Y position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo, and

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl,

phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents.

64. A method according to claim 63, wherein said disease condition is cerebral ischemia, chronic neurodegeneration, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of respiration, motor control and function, attention deficit disorders, concentration disorders, pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, eating disorders, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia or astrocytomas.

65. A method according to claim 64, wherein said mood disorder is anxiety, depression, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, or Alzheimer's disease.

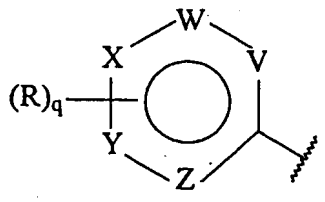
66. A method according to claim 64, wherein said extrapyramidal motor function is Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, or tardive dyskinesia.

67. A method according to claim 64, wherein said pain disorder is neuropathic pain, chronic pain, acute pain, painful diabetic neuropathy, post-herpetic neuralgia, cancer-associated pain, pain associated with chemotherapy, pain associated with spinal cord injury, pain associated with multiple sclerosis, causalgia and reflex sympathetic dystrophy, phantom pain, post-stroke (central) pain, pain associated with HIV or AIDS, trigeminal neuralgia, lower back pain, myofacial disorders, migraine, osteoarthritic pain, postoperative pain, dental pain, post-burn pain, pain associated with systemic lupus, entrapment neuropathies, painful polyneuropathies, ocular pain, pain associated with inflamation or pain due to tissue injury.

68. A method for preventing disease conditions in a subject at risk thereof, said method comprising:

administering to said subject a therapeutically effective amount of at least one compound having structure **A — L — B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein :

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of **V, W, X, Y and Z** is $(CR)_p$, wherein p is 0, 1 or 2;

at least one of **V, W, X, Y and Z** is O, N or S;

the remainder of **V, W, X, Y and Z** are each independently O, N or S; and

each **R** is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded:

the compounds wherein **A** is a 6-membered ring wherein:

V, W, X and **Y** are $(CR)_p$, wherein p is 1;

Z is N;

R at the V position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at the W position is hydrogen; R at the X position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Y position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

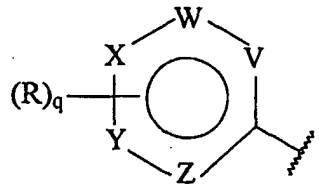
L is substituted or unsubstituted alkenylene, alkynylene or azo, and

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents.

69. A method according to claim 68, wherein said disease is a disease of the pulmonary system, a disease of the nervous system, a disease of the cardiovascular system, a disease of the gastrointestinal system, a disease of the endocrine system, a disease of the exocrine system, a disease of the skin, cancer or a disease of the ophthalmic system.

70. A pharmaceutically acceptable salt form of a compound, said compound having the formula **A — L — B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, wherein :

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of **V, W, X, Y and Z** is $(CR)_p$, wherein p is 0, 1 or 2;

at least one of **V, W, X, Y and Z** is O, N or S;

the remainder of **V, W, X, Y and Z** are each independently O, N or S; and

each **R** is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl; and

the salt is acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, heptanoate, hexanoate, 2-

hydroxyethanesulfonate, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, tartrate, toluenesulfonate, undecanoate, sulfate, bisulfate, hemisulfate, hydrochloride, hydrobromide, hydroiodide, an ammonium salt, an alkali metal salt, an alkaline earth metal salt, a dicyclohexylamine salt, *N*-methyl-D-glucamine, phenylethylamine, or an amino acid salt;

provided, that the following compounds are excluded: the compounds wherein **A** is a 6-membered ring wherein:

V, **W**, **X** and **Y** are $(CR)_p$, wherein p is 1;

Z is N;

R at the V position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at the W position is hydrogen; R at the X position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Y position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo, and

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents.

71. The pharmaceutically acceptable salt form of the compound, wherein the salt is a toluene sulfonic acid salt.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 00/23923

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/22 C07D277/24 C07D277/40 C07D213/16 C07D213/30
C07D239/26 C07D263/32 C07D271/06 C07D241/12 C07D249/08
C07D285/00 C07D333/08 C07D417/06 C07D409/06 C07D407/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 02497 A (NOVARTIS ERFINDUNGEN VERWALTUN ;HECKENDORN ROLAND (CH); AUBERSON Y) 21 January 1999 (1999-01-21) the whole document ---	1-71
Y	GASPARINI ET AL: "2-methyl-6-(phenylethynyl)-pyridine (MPEP): A novel potent, subtype-selective and systemically active antagonist at metabotropic glutamate receptor subtype 5" BRITISH JOURNAL OF PHARMACOLOGY,GB,BASINGSTOKE, HANTS, vol. 126, no. SUPPL. PROC, March 1999 (1999-03), page 249P XP002128760 ISSN: 0007-1188 the whole document --- -/--	1-71

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 2000	02/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr I Application No
PCT/US 00/23923

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/06 C07D401/06 C07D417/14 A61K31/425 A61K31/44 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VARNEY M A ET AL: "SIB-1757 AND SIB-1893: SELECTIVE, NONCOMPETITIVE ANTAGONISTS OF METABOTROPIC GLUTAMATE RECEPTOR TYPE 5" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,US,AMERICAN SOCIETY FOR PHARMACOLOGY AND, vol. 290, no. 1, July 1999 (1999-07), pages 170-181, XP000872672 ISSN: 0022-3565 the whole document	1-71
X	WO 96 03406 A (AGOURON PHARMA) 8 February 1996 (1996-02-08) example 1d	63,68,70

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; VARNEY, MICHAEL D. ET AL: "Protein Structure-Based Design, Synthesis, and Biological Evaluation of 5-Thia-2,6-diamino-4(3H)-oxopyrimidines: Potent Inhibitors of Glycinamide Ribonucleotide Transformylase with Potent Cell Growth Inhibition" retrieved from STN Database accession no. 127:130445 XP002153771 RNs 160743-80-6,160743-93-1,160744-06-9,193064 -71-0 & J. MED. CHEM. (1997), 40(16), 2502-2524 , ---	63,68,70
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHIH, CHUAN ET AL: "Synthesis and biological activity of acyclic analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid" retrieved from STN Database accession no. 116:151700 XP002153772 RN 137793-36-3 & J. MED. CHEM. (1992), 35(6), 1109-16 , ---	63,68,70
A	VARNEY ET AL: "Characterization of SIB-1757 and SIB-1893: Highly selective antagonists a metabotropic glutamate receptor subtype 5" BRITISH JOURNAL OF PHARMACOLOGY,GB,BASINGSTOKE, HANTS, vol. 126, no. SUPPL. PROC, March 1999 (1999-03), page 248P XP002128759 ISSN: 0007-1188 the whole document -----	1-71

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-71 relate to an extremely large number of possible compounds, salts and compositions. In fact, the claims contain so many options, variables, possible permutations and, particularly, provisos that support within the meaning of Article 6 PCT (claims) and disclosure within the meaning of Article 5 PCT (description) is to be found, however, for only a very small proportion of the claimed compounds. In the present case, the claims so lack support and the application lacks disclosure that a meaningful search over the whole of the claimed scope is impossible.

A formula consisting virtualiy of variables (which are moreover in at least part of the claims ill-defined (see, for instance, the use of unspecified "aryl", "heterocycle", "hydrocarbyl", etc, which can be possibly "substituted") cannot be considered as a definition of a patentable subject-matter. As a matter of principle, a formula consisting virtually completely of variables is hardly a permissible generalisation which is fairly based on experimental evidence. It is impossible to determine which part of the claim(s) may be said to define a subject-matter for which a protection might be legitimately be sought. All potential novel and inventive subject-matter is hidden in this large amount of possible compounds. Furthermore, in a "structure" like A-L-B, it does not appear straightforwardly to the skilled person what is to be considered as a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art.

In this respect, the large disclaimers are also sources of uncertainty since they do not define positively the subject-matter for which a protection is searched but, on the contrary, negatively and without giving in the description any commentary, reason or prior art knowledge in connection with these exclusions.
Furthermore A is said to represent a 5-, 6- or 7-membered ring, but this is in contradiction with the figure itself which includes the usual aromatic symbol (an internal circle in a hexagon) and is not appropriate for most of 5- and 7-membered rings which cannot be aromatic. It is also noted that some examples like 49, 50 and 64 do not fall in the scope of claim 1.
On the other hand, example 166 appears to belong to the first disclaimer and therefore is not to be considered as an illustration of the invention. Such inconsistencies add to the difficulty in determining the subject-matter for which a protection is sought.

Consequently, the search had to be carried out only in part. For determining the scope of a meaningful international search due account has been taken of PCT rule 33.3 and PCT search guidelines, III-2.1, 2.3 in conjunction with 3.7: special emphasis was put on those parts of the application which appear illustrated by the examples, i.e. wherein A represents a monocyclic 5- or 6-membered heteroring, L represents an ethynyl or a 1,2-propadienyl chain link and B can be a ring, benzyl, methanol, methanolsulfonate or hydroxymethylphenyl.

In spite of these restrictions, the inital phase of the search revealed a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

very large number of documents likely to be relevant to the issue of novelty (compounds per se). Consequently the search has been additionally limited to the domain of the claimed activity based on the given tests, that is, the modulation of the activity of metabotropic glutamate receptor 5 (mGluR5).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr al Application No
PCT/US 00/23923

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902497 A	21-01-1999	AU 8974398 A	08-02-1999
		BR 9811685 A	19-09-2000
		CN 1262676 T	09-08-2000
		EP 0998459 A	10-05-2000
		NO 20000124 A	02-03-2000
		SK 232000 A	12-06-2000
		ZA 9806137 A	22-01-1999
WO 9603406 A	08-02-1996	US 5608082 A	04-03-1997
		AU 697138 B	24-09-1998
		AU 3151795 A	22-02-1996
		CA 2195420 A	08-02-1996
		EP 0773943 A	21-05-1997
		FI 970317 A	05-03-1997
		JP 10503762 T	07-04-1998
		NO 970349 A	12-03-1997
		NZ 290703 A	25-11-1998
		US 5646141 A	08-07-1997